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Treatment of Adrenal Insufficiency

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THE INTRODUCTION of desoxycorticosterone for the treatment of Addison's disease was a significant advance in medicine (62). This hormone tends to correct the abnormalities in the salt and water content of the body and, secondarily, other abnormalities, but it does not provide for two of the major functions of the adrenal cortex: (a) gluconeogenesis and (b) androgenic function. Since both of these hormonal effects are eminently concerned with muscle function (see discussion), it is not surprising that many patients with adrenal insufficiency complain of weakness and easy fatigability in spite of adequate doses of desoxycorticosterone.

Corticosterone and allied substances, by their ability to promote conversion of protein to carbohydrate, protect against hypoglycemia and depletion of liver and muscle glycogen. In so doing these hormones increase the strength and exercise tolerance of adrenalectomized animals. They have other advantageous effects, such as the prevention of water intoxication. However, the expensiveness of corticosterone has prohibited its prolonged use in adequate quantities in the treatment of adrenal insufficiency.

Since the adrenal cortex secretes androgenic substances, which are concerned with muscle development, it is desirable to investigate the effect of these compounds on Addison's disease. The unavailability of potent androgenic substances of adrenal origin and also the demonstration of the pronounced myosthenic[2] effects of testosterone led to the

[1] Dr. Weinglass died January 3, 1945.

[2] The frequent necessity for reference in this paper to the muscle strengthening effect of various chemicals makes it desirable to have one word to express this idea. The word

use of testosterone in the treatment of the adrenal insufficiency of Simmonds' disease (68). Five patients with this disease were treated with the following four substances: methyl testosterone, testosterone pellets, desoxycorticosterone pellets, and desiccated thyroid. A marked improvement resulted in each patient; the increase in strength was particularly gratifying. In the present report is given the subsequent clinical response of all these five patients with Simmonds' disease, as well as the results of treatment of another such patient; metabolic studies were conducted in two of the patients. The results of comparable investigations in five patients with Addison's disease are given; metabolic studies were conducted in four of these cases.

The primary aim of therapy in these cases is the production of marked clinical improvement, as manifested by an increase in the patient's sense of well-being and in his work performance. Such an evaluation is sometimes difficult and requires a long time but some index of the probable effectiveness of the hormones can be readily obtained by estimating their effect on various chemical constituents of the body, as for example, the effect on nitrogen metabolism.

TABLE 1. SIGNIFICANT CLINICAL DATA

Case No.	Etiology	Age Yrs.	Sex	Duration of symptoms. Years	Weakness	Pigmentation	Adrenal crisis	Blood pressure mm. Hg.	Serum sodium m.eq/l	17-Ketosteroids mg./day	Insulin sensitivity	Follicle stimulating hormone R.U./day	B.M.R. Per cent	Plasma iodine γ/100 cc.	X-ray of sella turcica
								Simmonds' Disease							
1	Postpartum necrosis	42	F	12	++++	0	+	90/50	133	0.3	Incr.	0	−43	1	Neg.
2	Chromophobe adenoma	46	M	5	++++	0	+	74/65	127	2.5	Incr.	0	−36	—	Enlargement, destruction
3	Chromophobe adenoma	37	F	5	+++++	0	+	90/60	127	0.4	Incr.	0	−30	—	Enlargement, destruction
4	? Thrombosis	60	F	8	+++	0	+	100/65	136	1.4	Incr.	0	−33	3	Neg.
5	? Syphilis	45	F	20	++++	0	+	105/75	127	0.2	Incr.	0	−32	—	Neg.
6	Chromophobe adenoma	42	M	1	++	0	0	82/60	—	0	Incr.	0	—	—	Enlargement, destruction
								Addison's Disease							
7	?	41	M	1	+++	+++	0	90/60	131	3.1	Incr.	—	−10	7.2	Neg.
8	Tuberculosis	44	M	4	+++	++++	+	60/40	119	1.0	—	—	−41	2.0	Neg.
9	?	43	F	1	+++++	++++	+	88/60	130	1.5	Incr.	—	−29	2.8	Neg.
10	?	36	F	1	+++++	++++	+	80/55	129	0	Incr.	—	−14	—	Neg.
11	? Tuberculosis	38	M	3	+++	+++	+	106/64	133	2.0	Incr.	+ (96 R.U.)	−26	—	Neg.

METHOD OF STUDY

The diagnosis of Simmonds' disease or Addison's disease was clearly established in all 11 cases, with the exception of *Case 4* in which there was some uncertainty about the diagnosis of Simmonds' disease. Five of the patients were males and six were females. In each case weakness was an outstanding complaint. The six patients with Simmonds' disease had lost no significant amount of weight, but all five of the subjects with Addison's disease had experienced a distinct loss in weight. The individuals with Addison's disease were markedly pigmented, but there was no significant pigmentation in the other subjects. Nine patients had experienced adrenal crises. All patients had hypotension and a very small excretion of 17-ketosteroids (table 1). The serum sodium concentration, measured in ten cases, was low in each. In the ten cases in which an insulin tolerance test was performed, insulin sensitivity was found in each. The basal metabolic rate, tested in ten cases, was subnormal in eight. The protein-bound iodine, determined in five patients (including three with Addison's disease), was definitely subnormal in four. Roentgenograms of the sella turcica indicated normal structure in all of the patients with Addison's disease and in three with Simmonds' disease, whereas in three of the latter group there was enlargement and destruction of the sella, which was considered to be due to pituitary tumor. As far as could be ascertained, none of the patients had any primary disease of the kidneys, liver, gastro-intestinal tract or any other site

myosthenic was chosen, the prefix *myo* and the suffix *sthenic* being of Greek origin and meaning *muscle* and *strength*, respectively.

which would interfere with the metabolic studies.

Observations were made of the effects of methyl testosterone,[3] testosterone pellets and intramuscular injections of testosterone propionate. The effects of androstanediol, methyl androstanediol, and stilbestrol dipalmitate were also studied, the last one having been shown to increase the glycogen content of the liver. We wished to learn the effects of these substances in patients who were treated optimally with desoxycorticosterone, in those given inadequate doses, and in others given none. Some patients were given several different hormonal preparations, with only short intervals between, in order that the effects might be compared in the same individual when the disease was in approximately the same stage.

All metabolic balance studies were performed with the patients in a special ward in the hospital. The individuals were not confined to bed. No restriction of the fluid intake was imposed. The diet was usually the same each day throughout the period of study, although in some instances two isocaloric diets were given on alternate days. The elements of the diet were obtained in large quantities before the balance studies were begun, in order to help insure a uniform intake of food. Extra sodium chloride, usually in 4 gm. amounts, was given daily and the patient was required to take all of it regardless of the desires of his appetite. The balance study was not begun until the patient had been on the standard regimen for from 5 to 12 days. Urine specimens were saved in 24-hour amounts, with glacial acetic acid as a preservative except when specimens were collected for the estimation of the 17-ketosteroids; in this event concentrated hydrochloric acid was used. Blood was drawn from the fasting patient during the morning the regimen was to be changed.

Estimations were made of the excretion in the urine of sodium,[4] chloride, potassium, nitrogen, creatine, creatinine and 17-ketosteroids. Changes in the concentration in the blood of sodium, chloride, potassium, sugar, non-protein nitrogen, and carbon dioxide combining power were estimated in most cases. Insulin tolerance tests were conducted in all but one patient.

Daily estimations of the blood pressure, weight and strength were made, the last being tested with a hand dynamometer.

RESULTS OF STUDY

Case 1 (no. 1047166). H.O., a housewife, aged 42, was admitted to the hospital in May, 1941. The history, physical examination and laboratory studies were those of a classical example of panhypopituitarism, the onset having been associated with a stormy post-partum course 12 years previously. In December, 1941, therapy with methyl testosterone, desoxycorticosterone acetate, and desiccated thyroid was started. After several weeks two pellets of testosterone, 150 mg. each, and a pellet of desoxycorticosterone were implanted. Thyroid was given in doses of 64 mg. daily.

With this therapy there was a remarkable improvement in the general appearance, energy, strength and sense of well-being of the patient, the changes having begun to appear within a few days after the institution of the combined therapy and continuing for several months. The eyebrows, as well as the hair on the scalp, axillae, arms and pubis showed moderate growth. The blood pressure, previously low, was maintained at a normal level. Anorexia and the occasional attacks of nausea, vomiting and abdominal cramps disappeared, although she continued to experience an occasional episode of hypoglycemia in spite of eating frequently throughout the day. Most of the manifestations of myxedema disappeared. No complications from the therapy resulted, other than the appearance of a small amount of fuzzy hair on the cheeks and upper lip.

[3] The methyl testosterone (Metandren) used was supplied by the Ciba Pharmaceutical Products, Inc., Summit, N. J. This company also supplied perlingual methyl testosterone (Metandren Linguets), pellets of desoxycorticosterone acetate (each weighing approximately 125 mgm.), androstanediol 3α, 17α, methyl androstanediol 3α, 17α, and testosterone propionate (Perandren). The pellets of testosterone (Oreton F) were supplied by the Schering Corporation, Bloomfield, N. J. These pellets weighed 75 or 150 mgm. All pellets were implanted subcutaneously lateral to the breast. All desiccated thyroid conformed to the U.S.P.

[4] The methods used for the analyses are as follows: sodium, Butler and Tuthill (8) as modified by Consolazio and Dill (9); urine chloride, Wilson and Ball (69); plasma chloride, Keys (42); potassium, Shohl and Bennett (57), as modified by Consolazio and Talbott (10); nitrogen, Gunning, (22) and Arnold and Wedemeyer (3); creatine and creatinine, Folin and Wu (15); 17-ketosteroids, Talbot, Butler and MacLachlan (59); total serum protein, Kagan (33); sugar, Folin and Wu (16); carbon dioxide combining power, Van Slyke and Cullen (65); glucose-insulin tolerance test, Fraser, Albright and Smith (18).

During the year following the implantation of the pellets the patient was seen at monthly intervals. After about from eight to ten months a slight reduction in strength began to appear. Her friends observed a "slowing-up" in her mental and physical activities, in spite of the fact that she continued to take 64 mg. of thyroid daily. Puffiness of the skin returned. All of the axillary hair and most of the pubic hair disappeared again. She became weak, dizzy and vomited once. After three days of moderate weakness she returned to the hospital, in April, 1943, one year after the pellet therapy was started. The same dosage of desiccated thyroid was continued and she was placed on a diet containing 1400 calories per day, in the proportions of 54 gm. of protein, 133 gm. of carbohydrate, 53 gm. of fat; there were 33 m.eq. of sodium and 28 m.eq. of potassium. This low-calorie diet was chosen by the patient as she did not feel confident of eating more than this amount. After a period of standardization and two control periods of four days each, testosterone propionate was given intramuscularly in doses of 25 mg. per day for eight days, followed by two similar periods without treatment. During the intervals of treatment and for several days thereafter a marked improvement in the patient resulted. She experienced an increase in appetite, energy, strength and feeling of well-being. Dynamometer estimations showed about a 35 per cent increase in strength (fig. 1) which persisted for at least eight days after discontinuation of the ther-

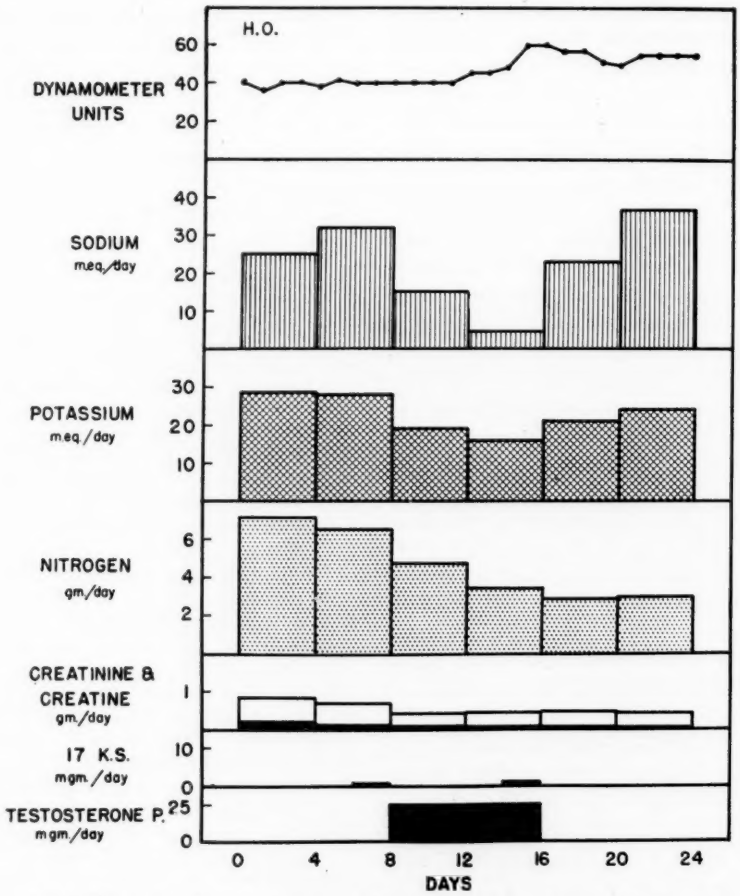

FIG. 1. Response in *Case 1* to treatment with testosterone propionate while the patient was maintained on a constant diet. The strength was measured with a hand dynamometer. In the columns are recorded the average daily excretion in the urine of sodium, potassium, nitrogen, creatinine and creatine. The excretion of 17-ketosteroids (17 KS) is also charted.

apy. No change in the weight resulted and the blood pressure remained normal. Testosterone propionate caused a pronounced retention of sodium, potassium, nitrogen, and creatinine, which persisted for a number of days after cessation of treatment. Essentially no change resulted in the excretion of 17-ketosteroids in the urine.

Since no pellets of testosterone were available, she was discharged from the hospital in May, 1943, taking 30 mg. of methyl testosterone, daily. With this therapy she continued in good condition. In September, 1943, one pellet of desoxycorticosterone acetate was implanted. In October she discontinued the methyl testosterone therapy, following which she noticed a decrease in strength and energy, but with resumption of this therapy, in November, she experienced a distinct improvement.

In January, 1944, she was brought into the hospital in a semi-stuporous state; she had developed pneumonia in the left lower lobe. She had voluntarily discontinued the thyroid and methyl testosterone therapy one month previously. Two weeks before admission she developed a rhinitis and bronchitis. When suffering from respiratory infections she had previously coöperated by taking an additional 4 gm. of sodium chloride daily, but she disregarded the prescription on this occasion. On admission her blood pressure was 90/60. The temperature was 102.4° F. In spite of treatment with adrenal cortical extract, desoxycorticosterone, testosterone propionate, sulfathiazole, frequent infusions of glucose and saline, and general supportive measures the patient died four days after admission.

At autopsy the pituitary gland was found to be

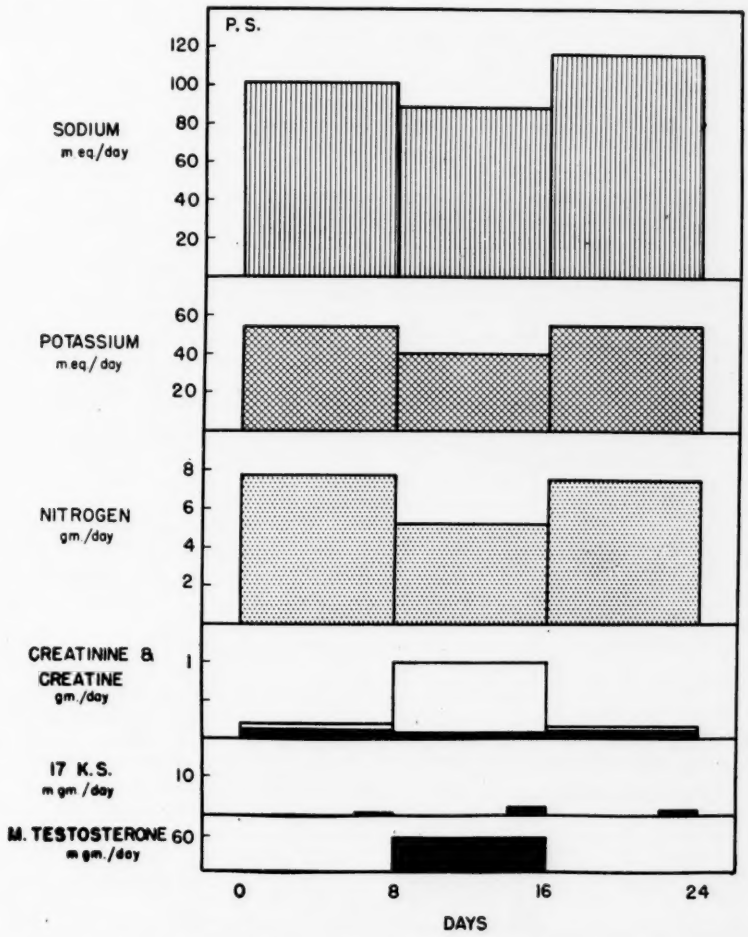

FIG. 2. Response in *Case 2* to treatment with methyl testosterone.

very small and it was composed almost entirely of fibrous tissue with a very few nests of basophilic acini and some colloid-filled cysts. A small portion of the pars nervosa was present. The thyroid gland was quite small; it consisted chiefly of fibrous tissue with a few small follicles relatively devoid of colloid. Extensive search failed to reveal the presence of the adrenals. The ovaries were small and fibrotic. The pancreas and the parathyroid glands were not remarkable.

Case 2 (*no. 1047262*). *P.S.*, a white laborer, aged 46, was admitted to the hospital in August, 1941. The history and physical examination suggested that he had Simmonds' disease, and the laboratory data gave strong support to this diagnosis. A chromophobic adenoma was regarded as the probable cause of the disease and roentgenotherapy was applied to the pituitary region. In December, 1941, he began the treatment with desiccated thyroid, desoxycorticosterone acetate and methyl testosterone. The marked improvement in the ensuing weeks prompted the implantation of five pellets of desoxycorticosterone acetate and three pellets of testosterone, each of the latter weighing 150 mg. The remarkable improvement in the ensuing few months has already been reported (68). He was subsequently seen in the Out-patient Department at intervals of from one to two months.

In September, 1942, he began to notice a slight decrease in strength; however, upon taking 30 mg. of methyl testosterone daily he regained some of his former vigor.

In March, 1943, he was readmitted to the hospital for study. His general condition was good, and he was fed a diet yielding 1916 calories, composed of 85 gm. of protein, 160 gm. of carbohydrate, 104 gm. of fat, 120 m.eq. of sodium and 55.6 m.eq. of potassium. After a control period of eight days he was given 60 mg. of methyl testosterone, divided into three doses daily for eight days. A distinct increase in strength and energy was noted two days after the therapy was started. There was retention of sodium (fig. 2), potassium and nitrogen, and there was a marked increase in the amount of creatinine excreted. No significant effect on the creatine or the 17-ketosteroid excretion was observed. There was no change in the patient's weight; the blood pressure remained normal.

In the spring of 1943, and during the subsequent year and a half, his therapy in addition to the 96 and 128 mg. of thyroid was methyl testosterone in doses of 30 mg. daily; extra salt was added as indicated during respiratory infections and also during the summer. Intervals of two to three months elapsed when he was financially unable to secure the methyl testosterone. During each of these periods there was a definite decrease in strength, energy, and ambition, but on each occasion there was a rapid amelioration of symptoms following the resumption of therapy. However, not as much improvement resulted with doses of 30 mg. as with 50 or 60 mg., nor did he feel quite as well with the latter as during the four or five months after the implantation of the three pellets of testosterone, mentioned above.

In February and March, 1944, he occasionally felt dizzy, weak, and complained of anorexia. There was also a slight drop in his blood pressure. These changes persisted in spite of 4 to 8 gm. of extra sodium chloride daily and methyl testosterone, 30 mg. daily. In April, 1944, two pellets of desoxycorticosterone, 125 mg. each, were implanted; a distinct improvement of the patient resulted. Within a few weeks edema developed, but this disappeared with the cessation of sodium chloride therapy. In October, 1944, three pellets of testosterone, 75 mg. each, were implanted.

During the three years of treatment the patient had gained 25 pounds in weight. The visual fields, which were narrowed at first, are now normal. There has been no apparent destruction of the sella turcica; he has maintained a moderately heavy beard and some axillary and pubic hair which developed in association with androgen therapy, and he has performed a moderate amount of work.

Case 3 (*no. 1048285*). *D.N.*, a female artist, aged 37, was admitted in May 1941. She was regarded as having Simmonds' disease resulting from a chromophobe adenoma. Her therapy was similar to that outlined in the two previous cases; essentially all of the results were reported previously (2). After having apparently been in very good general condition until the day of her death, she died at home after an illness of a few hours about six months after therapy was started. The cause of death was apparently a hypoglycemic reaction, but no opportunities were afforded for diagnosis either by clinical measures or by necropsy.

Case 4 (*no. 1058888*). *I.D.*, an unmarried white woman, aged 60, was admitted to the hospital in January, 1942. She had been treated for the previous eight years for myxedema and pernicious (?) anemia. The patient was diagnosed as having Simmonds' disease on the basis of the following: the picture of myxedema, which had not responded satisfactorily to prolonged treatment with thyroid; the hypersensitivity to insulin; the small quantity of 17-ketosteroids excreted in the urine; the low concentration of serum sodium; a negative test for follicle-stimulating hormone in the urine (tested for 20 R.U. per 24 hours); and the clinical manifestations of adrenal insufficiency. She was treated with 92 mg. of desiccated thyroid daily, two pellets of desoxycorticosterone acetate and one of testosterone (150) mg.). She experienced a marked general improvement with a distinct increase in strength. However, within a month the development of dyspnea and hypertension led to the removal of one of the desoxycorticosterone pellets. The dyspnea and hypertension diminished, but within another two months the blood pressure had risen to 190 mm. systolic and 100 mm. diastolic, and there was moderate dyspnea.

Consequently, the remaining pellet of desoxycorticosterone was removed. Improvement of the patient was apparent within a few days, but one month later she developed manifestations of a cerebral thrombosis, signs of which subsided in a few days. Throughout the last two years she has been seen at intervals of one to two months. Aside from headaches, slight dyspnea and episodes suggesting hypoglycemia, she has felt relatively well. She developed fairly good strength and a normal amount of axillary and public hair. In September, 1944, she was admitted to the hospital for re-evaluation. Although she had had no thyroid treatment for ten weeks, she had no definite evidence of myxedema and her basal metabolic rate was −3. The insulin tolerance test, performed in the same manner as in 1942, showed distinctly less insulin sensitivity than earlier. The 17-ketosteroid excretion which was 1.4 mg. per 24 hours in 1942, was 3 mg. The F.S.H. test, which was negative to 20 R.U. in 1942, was positive. The "water test" was positive. Therefore, the patient showed a definite improvement in her glandular functions.

Case 5 (*no. 764228*). *F.S.*, a housewife, aged 45, was admitted to the Massachusetts Memorial Hospital[5] in December, 1941. After the diagnosis of Simmonds' disease was established her therapy was 92 mg. of desiccated thyroid daily and the implantation of two pellets each of desoxycorticosterone and testosterone (150 mg. each). The patient experienced a marked improvement in strength and general well-being, but after about eight months there occurred some loss of strength. She did not return for observation very often, but continued taking thyroid regularly. In November, 1943, she was admitted to the Boston City Hospital for replenishment of therapy. She exhibited many features of chronic adrenal insufficiency. She was given 2 mg. of desoxycorticosterone acetate daily. After one week the dosage was reduced to 1 mg. and she was also given 25 mg. of testosterone propionate three times per week. Although some improvement was apparent within two days after the desoxycorticosterone therapy was started, there was a marked increase in strength and in energy within a few days after the testosterone was instituted. Unfortunately, two weeks after the latter therapy was started she developed virus pneumonia and died witin 24 hours.

At autopsy the pituitary was found to be very small. On microscopic examination there were found a few acidophilic, basophilic and chromophobic cells scattered in dense scar tissue. No etiologic lesions in the pituitary were observed. The thyroid gland was about one-half the normal size; the acini were atrophic. The adrenals were completely replaced by fibrous tissue. There was bronchopneumonia in each lower lobe.

[5] We are very grateful to Dr. Chester S. Keefer and his staff for their generous coöperation in the study of *Cases 5*, *9*, and *11*.

Case 6 (*no. 111478*). *G.M.*, a laborer, aged 42, was admitted to the hospital in June, 1943. He was found to have Simmonds' disease, which was apparently due to a chromophobe adenoma of the pituitary gland. Following an unsuccessful attempt to remove the tumor, roentgenotherapy was applied. There was no improvement in his endocrine functions, but there was some improvement in his visual fields. Beginning in March, 1944, he was given intramuscularly 25 mg. of testosterone propionate three times a week for six weeks. No other hormonal therapy was given.

During this treatment there was a marked increase in strength and a slight gain in weight. Pellets of testosterone are to be implanted.

Case 7 (*no. 1102778*). *J.C.*, a retired fireman, aged 42, was admitted to the hospital in April, 1942, with Addison's disease, which he apparently had had for more than a year.

On the day after admission he began receiving desoxycorticosterone acetate intramuscularly, and this was given daily until the amount necessary to maintain the patient in good condition was ascertained. Four pellets of desoxycorticosterone acetate were implanted on July 6th.

Four pellets of testosterone, 75 mg. each, were implanted on April 30th. On the day preceding this treatment the 17-ketosteroid excretion was 2.5 mg.; on May 14th it was 2.6 mg. and June 17th it was 1.7 mg. On the first of June he began to take 64 mg. of desiccated thyroid daily.

With the foregoing treatment he experienced a marked improvement, but it was, of course, difficult to assess the value of each of the drugs used.

Following discharge from the hospital, in July, 1942, he was seen every one to two months in the Out-patient Department. At all times he was in good condition and was taking care of miscellaneous jobs satisfactorily. However, he sometimes had vague complaints, thought to be psychoneurotic. He also showed a lack of stamina.

In April, 1943, he was readmitted to the hospital for a check-up. He was found to be in relatively good condition, having no significant complaints, a normal blood pressure, good strength, and a normal concentration of serum sodium.

He was placed on a diet consisting of 2031 calories with 87 gm. of protein, 178 gm. of carbohydrate, 102 gm. of fat, 56 m.eq. of potassium, and 120 m.eq. of sodium. After a period of stabilization for five days and a control period of four days he was given intramuscularly 25 mg. of testosterone propionate daily for eight days. With this therapy there was no definite increase in strength and no change resulted in the hand dynamometric estimations; both before and during therapy the readings were 100 to 110, which gives evidence that his strength was as good as that of a normal man. During treatment there resulted a distinct retention of sodium (fig. 3), a slight retention of potassium, and a marked increase in the amount of 17-ketosteroids excreted. No signifi-

cant changed resulted in the creatine, or creatinine, excretion, but there was a slightly increased excretion of nitrogen.

His general condition was sufficiently good to warrant a delay in the replenishment of the pellets of desoxycorticosterone until January, 1944. He has remained in good condition and has been performing a moderate amount of work.

monthly intervals. He gained 10 to 20 pounds in weight and became stronger; his blood pressure remained essentially normal. Although he occasionally had spells of weakness and dizziness, most of the time he felt quite well. His muscular development, good state of nutrition and general appearance suggested that he should have the capacity for almost any type of work. He tried several jobs but did not

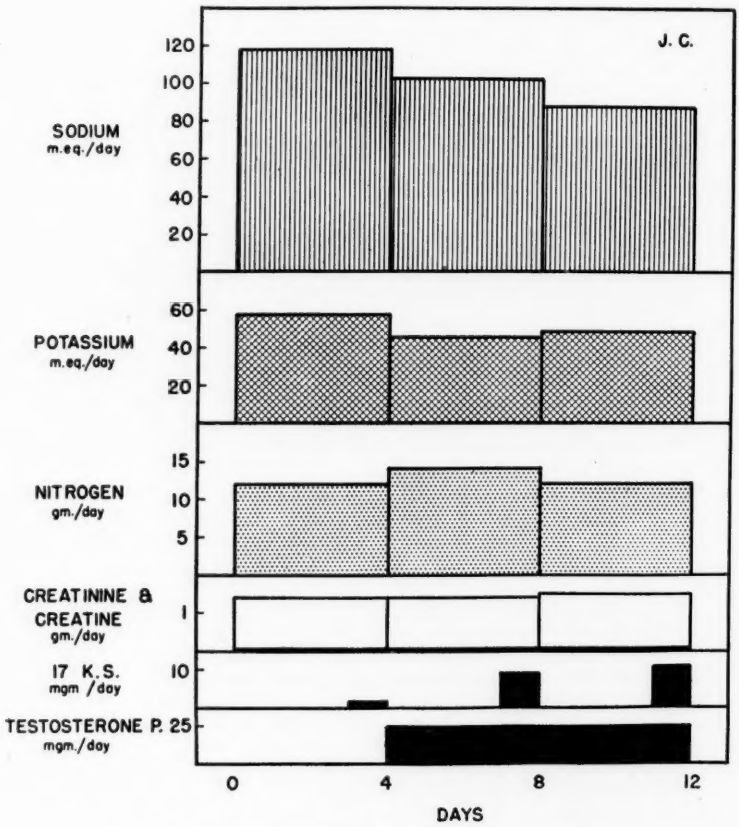

FIG. 3. Response in *Case 7* to treatment with testosterone propionate.

Case 8 (*no. 1080075*). *C.E.*, a laborer, aged 44, was admitted to the hospital in an Addisonian crisis in February, 1941. He had a history of Addison's disease for about four years or longer. Roentgenograms revealed the presence of calcification in the adrenals and many scattered plaques in the lungs, but no evidence of active tuberculosis. After several weeks of treatment with extra salt and intramuscular injections of desoxycorticosterone, four pellets of desoxycorticosterone were implanted. He was discharged from the hospital in April, 1941, and in the following year was seen in the Out-patient Department at

continue with any for longer than a few days or weeks. He stated that the work was "too hard" and that he soon became tired.

In June, 1942, he complained of having lost 18 pounds in weight in the two previous months. His strength also decreased. With the administration of 8 gm. of extra sodium chloride per day his symptoms definitely improved.

In August, 1942, he was readmitted for further study and treatment. At this time he had no complaint other than increased weakness in the previous month. His blood pressure was normal, as was the

serum sodium and potassium, but the 17-ketosteroid excretion was only 4 mg. per 25 hours. Two pellets of testosterone, 150 mg. each, and two pellets of desoxycorticosterone acetate were implanted. Estimation of the creatinine and nitrogen excretion for ten days before and 10 days during the testosterone treatment showed no change in the former and only slight retention of nitrogen. During the ensuing few weeks he felt stronger and better in general than he had felt before. About one month after the pellet treatment he developed slight edema, but this disappeared with elimination of extra sodium chloride.

His progress continued to be good until August, 1943, when he noticed more weakness than usual. His blood pressure was slightly low. However, definite improvement resulted with salt therapy.

In January, 1944, he was readmitted for study and further treatment. He had no specific complaints, other than a tendency for easy fatigability. His blood pressure was 100 mm. systolic and 70 mm. diastolic. The hematocrit, non-protein nitrogen, and fasting blood sugar were normal, but the serum sodium was 135 m.eq. per liter and the chloride 87 m.eq. per liter. The serum potassium was 4.7 m.eq. per liter.

He was fed on a diet calculated to yield 1937 calories, composed of 88 gm. of protein, 80 gm. of fat, 217 gm. of carbohydrate, 137 m.eq. of sodium, and 95 m.eq. of potassium. After 12 days a control period of eight days was run after which he was given 20 mg. of androstanediol four times daily for eight days. This was followed by another control period for eight days. In association with the treatment no changes resulted in the normal blood pressure, weight, or dynamometric estimations. However, a few days after the institution of therapy the patient felt somewhat stronger.

The androstanediol caused a retention of sodium

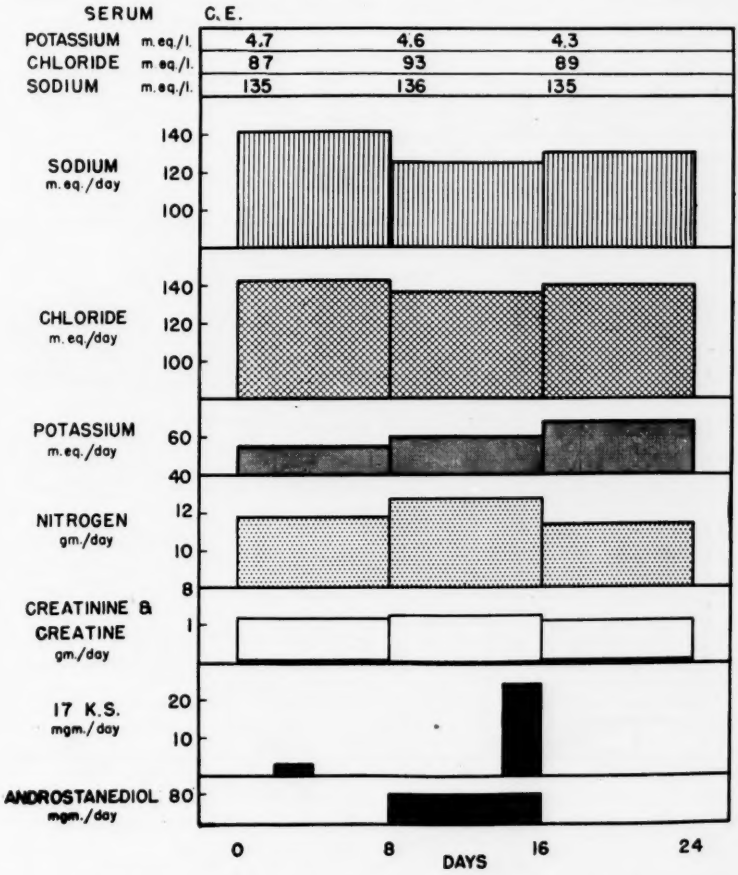

FIG. 4. Response in *Case 8* to treatment with androstanediol, 3α, 17α.

(fig. 4) and chloride but an increased elimination of potassium, nitrogen and creatinine. It produced a marked increase in the elimination of 17-ketosteroids. No significant change occurred in the values of the serum electrolytes.

On the completion of the metabolic study two pellets of desoxycorticosterone acetate were implanted. One month later five pellets of testosterone, 75 mg. each, were inserted. He obtained a job and

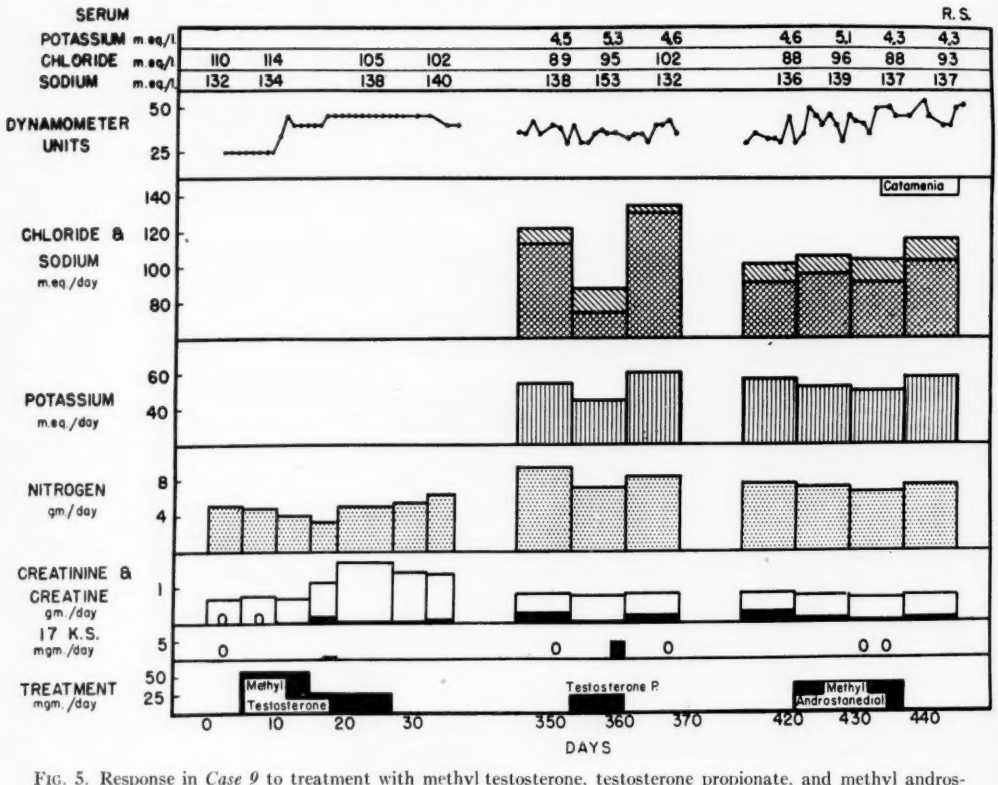

FIG. 5. Response in *Case 9* to treatment with methyl testosterone, testosterone propionate, and methyl androstanediol, 3α, 17α.

has now worked regularly for the past seven months, this being the longest interval of work in four years. During this time he has felt quite well and has had more strength than he has had at any other time in the last four or five years. He has maintained a normal blood pressure, weight and serum sodium concentration.

Case 9 (*no. 1125208*). *R.S.*, a housewife, aged 43, was admitted to the Massachusetts Memorial Hospital in September, 1942. She had shown manifestations of Addison's disease for about one year. The etiology of the disease was not known; there was no evidence of tuberculosis.

Within a few days after admission to the hospital she began receiving treatment for adrenal insufficiency. For the next three months she was given about 5 gm. of extra sodium chloride daily and 3 to 6 mg. of desoxycorticosterone. In December, 1942, while the patient continued to receive the foregoing treatment, the effects of methyl testosterone were studied. She was fed a constant diet; 60 mg. of methyl testosterone were given daily for 10 days, followed by 30 mg. for 12 days. Associated with this therapy there was a definite increase in the patient's strength, subjective and objective (fig. 5). The therapy caused a retention of nitrogen, but an increased elimination of creatinine and creatine. The serum sodium concentration increased, but there was no significant change in the 17-ketosteroid excretion. Following this balance study four pellets of desoxycorticosterone were implanted. However, about four weeks later the patient developed hypertension and subcutaneous edema which persisted in spite of sodium chloride restriction. The removal of one pellet corrected these complications.

Following discharge from the hospital in February 1943, she was seen at monthly intervals. She felt fairly well and did a moderate amount of housework. She maintained a normal blood pressure and

serum sodium, but at each visit she complained of weakness, easy fatigability and lack of energy.

In November, 1943, she was admitted to the Boston City Hospital for further treatment which was direct toward an improvement of her strength. Her clinical condition and serum sodium concentration were found to be relatively well regulated. She was fed a constant diet yielding 1577 calories, composed of 71 gm. of protein, 201 gm. of carbohydrate, 54 gm. of fat, 118 m.eq. of sodium and 81 m.eq. of potassium. Eight days were allowed for stabilization and another eight days, for a control period. Following this 25 mg. of testosterone propionate were injected, intramuscularly, daily for eight days. Within two or three days after this therapy was started the patient experienced a distinct increase in strength and energy as evidenced not only by her assertions but also by her activities on the ward. However, the dynamometric estimations revealed no significant change. During this therapy there was a marked retention of sodium and chloride. There was a moderate retention of nitrogen, potassium, and creatine. The 17-ketosteroid excretion changed from 0 to 5 mg. per day.

After the patient became stabilized she was given, intramuscularly, 10 mg. of stilbestrol dipalmitate daily, but after five days she was so sick that this therapy was discontinued. She developed nausea, vomiting, nervousness, hyperhidrosis and marked weakness. No change resulted in the excretion of sodium, chloride, nitrogen, creatine, or creatinine, but there was a slight retention of potassium. No 17-ketosteroids were excreted. Following this treatment about two weeks were required for the patient to return to her former condition. After this readjustment she was given, intramuscularly, 1 mg. of desoxycorticosterone acetate daily.

In order to study the effects of methyl androstanediol, she was again placed on a constant diet calculated to yield 1362 calories, composed of 65 gm. of protein, 160 gm. of carbohydrate, 51 gm. of fat, 107 m.eq. of sodium and 75 m.eq. of potassium. After a period of five days of standardization and a control period of eight days she was given 10 mg. of methyl androstanediol four times daily for 16 days. During this therapy there was a definite increase in strength, subjective and objective (fig. 5). There was a slight retention of potassium. nitrogen, creatinine and creatine, but no significant alteration in the excretion of 17-ketosteroids, sodium or chloride.

Twelve days after cessation of treatment with methyl androstanediol, one pellet of desoxycorticosterone acetate and three pellets of testosterone, 75 mg. each, were inserted.

She was discharged from the hospital on April 5, 1944. When next seen, on the first of June, she stated that her strength and energy were greater than before the hospitalization, but there was not as much improvement as was desired. For a period of six weeks, beginning the first of June, she was given daily 40 mg. of androstanediol. During this period of therapy there was a further increase in strength and in her sense of well-being. From July 15th to August 15th no additional treatment was given; the patient thought that there was a very slight loss of strength in this interval. During the latter half of August she was given 80 mg. daily of methyl androstanediol, without any definite effects. No extra therapy was administered from September 1st to October 15th, but during the subsequent month she was given daily 50 mg. of methyl testosterone linguets. There was only a slight increase in strength and energy associated with this.

Case 10 (no. 1124320). S.F., a housewife, aged 36, was admitted to the hospital in November, 1943. She had shown manifestations of Addison's disease for about seven months; she had not had any specific treatment. Five days before the metabolic study was started she was fed a constant diet calculated to yield 1420 calories, composed of 60 gm. of protein, 167 gm. of carbohydrate, 55 gm. of fat, 118 m.eq. of sodium, and 65 m.eq. of potassium. During a period of three months the effects of testosterone propionate, stilbestrol dipalmitate, androstanediol, and methyl androstanediol were tested. In this case it was decided to use a minimal amount of desoxycorticosterone acetate, in order to note the specific effect of the various drugs. However, it is to be emphasized that the kidney function was impaired more than it is in well treated cases of Addison's disease. On the day that the constant diet was started, the patient began receiving intramuscular injections of desoxycorticosterone acetate, 1 mg. daily. At the end of the seventh metabolic period the dosage was doubled.

Testosterone propionate was given, intramuscularly, in doses of 25 mg. daily for eight days. The therapy was associated with a distinct increase in the energy and strength of the patient. There was a decrease in the blood non-protein nitrogen, a slight increase in the excretion of sodium and chloride, and a slight retention of potassium, nitrogen, creatine and creatinine (fig. 6). No 17-ketosteroids were found in the urine preceding treatment, but with therapy there were 3.6 mg. per day.

Nine days after the cessation of testosterone propionate, 5 mg. of stilbestrol dipalmitate was given, intramuscularly, daily for six days. Two days after this therapy was started the patient complained of anorexia, nausea and pronounced weakness. These symptoms progressively increased and persisted for several days after the last injection. There was an increased excretion of sodium, chloride, nitrogen and creatine. At the time that the stilbestrol treatment was discontinued, a short insulin tolerance test, using 4 units of insulin intravenously, yielded blood sugar values as follows: fasting, 81 (mg./100 cc.); 30 min., 70; and 60 min., 71. When the same test had been conducted one month previously using 3 units of insulin the values were: fasting, 94; 30 min., 50; and 60 min., 62.

Ten days after cessation of the stilbestrol treatment, androstanediol was given, orally, in doses of 10 mg., four times daily for 16 days. About five days after the beginning of this therapy there was a definite increase in strength, subjective and objective (fig. 6). The patient displayed more energy than usual. The androstanediol did not cause any retention of sodium, chloride or potassium and caused no

also had primary hypogonadism, having had features of this condition most of his life. During adolescence he was obese, particularly in the middle third of his body. He never developed axillary or pubic hair or a beard. On examination his voice was found to be high-pitched and he was effeminate in his reactions. The arms and legs were long in proportion to the trunk; the testes and penis were small. There were

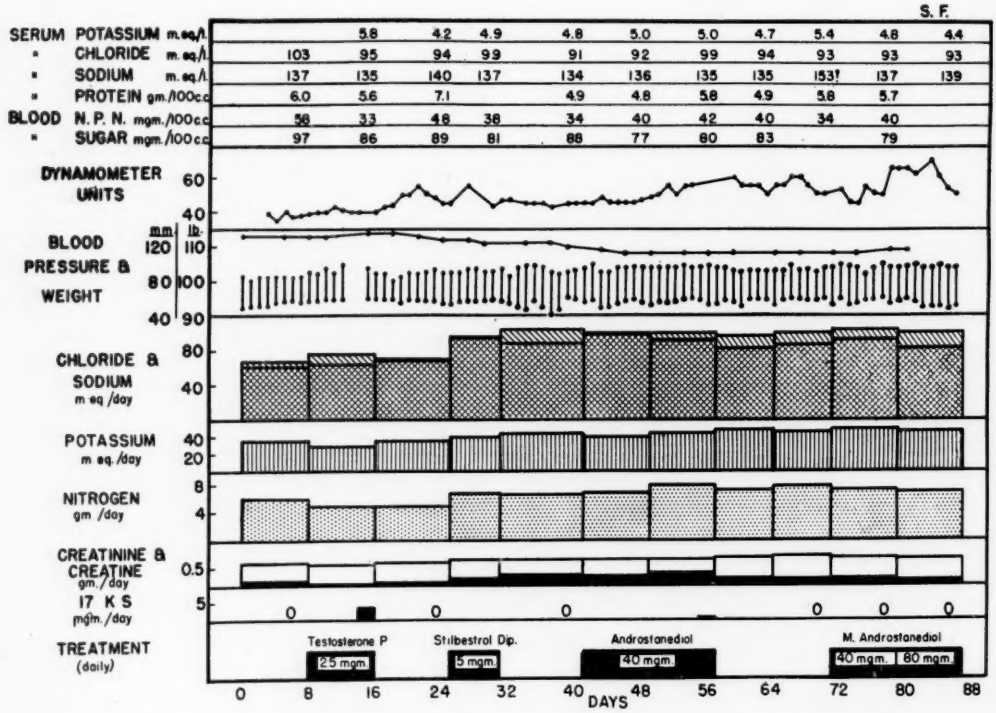
S. F.
SERUM POTASSIUM m.eq./l. 5.8 4.2 4.9 4.8 5.0 5.0 4.7 5.4 4.8 4.4
" CHLORIDE m.eq./l. 103 95 94 99 91 92 99 94 93 93 93
" SODIUM m.eq./l. 137 135 140 137 134 136 135 135 153! 137 139
" PROTEIN gm./100cc 6.0 5.6 7.1 4.9 4.8 5.8 4.9 5.8 5.7
BLOOD N. P. N. mgm./100cc 58 33 48 38 34 40 42 40 34 40
" SUGAR mgm./100cc 97 86 89 81 88 77 80 83 79
DYNAMOMETER UNITS
BLOOD PRESSURE & WEIGHT
mm lb.
CHLORIDE & SODIUM m eq /day
POTASSIUM m eq./day
NITROGEN gm /day
CREATININE & CREATINE gm./day
17 K S mgm./day
TREATMENT (daily)
Testosterone P 25 mgm.
Stilbestrol Dip. 5 mgm.
Androstanediol 40 mgm.
M. Androstanediol 40 mgm. 80 mgm.
DAYS

FIG. 6. Response in *Case 10* to treatment with testosterone propionate, stilbestrol dipalmitate, androstanediol, 3α, 17α, and methyl androstanediol, 3α, 17α.

significant increase in the 17-ketosteroid excretion. After an interval of 14 days without treatment the patient was given 10 mg. of methyl androstanediol four times daily for eight days and then 20 mg. four times daily for another eight days. With this therapy there was an increase in strength, subjective and objective, but no significant change in the excretion of sodium, chloride, nitrogen, creatine, creatinine or 17-ketosteroids. Throughout the entire period of study the blood pressure remained low and there was slight loss of weight.

On the completion of these studies four pellets of desoxycorticosterone were implanted.

Case 11 (no. 291751). C.R., a laborer, aged 38, was admitted to the Massachusetts Memorial Hospital in June, 1943, with Addison's disease, having had manifestations of this disorder for three years. He

96 rat units of follicle stimulating hormone in the urine per 24 hours.

After his condition had become somewhat stabilized by treatment with 8 gm. of sodium chloride daily, he was given 20 mg. of methyl testosterone three times daily for three days and then 10 mg. three times daily for seven days. During this treatment he gained five pounds, while in the previous week he had not gained. He also observed a definite increase in strength. About two weeks after cessation of the methyl testosterone therapy two pellets of testosterone, 75 mg. each, were implanted subcutaneously. The patient gained four pounds in the next five days, whereas he had not gained in the previous week; he also noted an increase in strength. He was discharged from the hospital in August, 1942, but follow-up studies were unsatisfactory.

DISCUSSION

In well defined cases of Addison's disease and Simmonds' disease the structure and functions of the adrenal glands are markedly reduced; this leads to a large number of abnormalities which may be clinically apparent. Most of the changes produced are presumably due to decrease in the steroids which are concerned with: (a) control of salt and water balance, (b) androgenic function, and (c) gluconeogenesis. All three factors would seem to be of importance in obtaining maximal performance of muscles. However, the question arises as to the relative importance of each factor. Although certain steroids isolated from the adrenal have predominantly one of the three actions mentioned, some direct or indirect effect on the other functions are also manifested.

Thorn and associates (62) found that with the use of desoxycorticosterone in the treatment of Addison's disease there resulted: (a) an increase in body weight; (b) an elevation of blood pressure; (c) an increase in plasma volume; and (d) a restoration of plasma concentration of sodium, chloride, and potassium to normal levels. With these changes there occurs: (a) an improvement in the absorption of substances from the gastro-intestinal tract, (b) a slight increase in the basal metabolic rate, and (c) an improvement in strength and well-being.

In spite of the beneficial effects of desoxycorticosterone the patients tend to complain of weakness and easy fatigability, even when receiving optimum treatment with this hormone. They also exhibit a deficient capacity to make adequate readjustments in the face of trauma, infections, or radical changes in salt and water metabolism (58). Moreover, they may die of hypoglycemia. Therefore, it is desirable to administer additional therapy; in this connection androgen therapy is now considered.

Although there is not much direct proof that the adrenal cortex produces androgens in normal individuals, there is a great deal of indirect evidence that such is the case (44). Furthermore, in individuals with adrenal neoplasms large quantities of androgens have been found in the urine.

Reichstein (51) obtained adrenosterone from the adrenal cortex, and Mason and associates (49) prepared the same substance by the oxidation of Kendall's Compound E. In rats and mice gonadectomy causes adrenal hypertrophy in the male, although atrophy results in the female. This hypertrophy is associated with androgenic secretion from some source as evidenced by the continued development of the prostate in the immature castrated rat. If the adrenals are also removed the prostate does not develop. The characteristic x-zone in the adrenal of normal female mice is associated with androgenic activity. It develops in the castrated male mouse in the absence of male hormone therapy, but testosterone injection prevents this development.

Females as well as males excrete androgens in the urine. Both sexes continue to excrete this material after gonadectomy, although in reduced amounts, particularly in males. Females with Addison's disease excrete little, if any, androgens in the urine (44, 19).

Patients with marked adrenal insufficiency tend to have aplasia of axillary and pubic hair. Males commonly have testicular atrophy.

Granting, then, that hypoandrogenism is commonly associated with adrenal insufficiency, the next point to establish is to what extent this deficiency is associated with the persistent weakness experienced by the individuals with this disease. The effects of testosterone are first considered since this substance has a much stronger androgenic effect than any other substance known (44). Whereas testosterone has not been shown to be derived from the adrenal, the latter apparently has the capacity to produce a testosterone-like substance, as evidenced by the clinical and laboratory data in classical cases of the adrenogenital syndrome. Furthermore, in males there is a possibility that the adrenal is concerned in the manufacture of testosterone precursors. Thus far, bulls' testicular tissue is the only material from which testosterone has been prepared in pure form.

Hoskins (24) found that castration diminished by about 60 per cent the voluntary activity of male rats. On the other hand, treatment with androgens increased the voluntary activity of castrated rats. Papanicolaou and Falk (50) found that testosterone caused muscle hypertrophy in guinea pigs. It has been known for a long time that eunuchs lack strength, energy and stamina. However, these handicaps can be largely removed with testosterone therapy. Testosterone propionate causes a depression in the urinary excretion of nitrogen, inorganic phosphorus, sulfate, sodium, potassium and chloride (28, 37, 40, 41, 43, 45). Creatine excretion, when substantial, may be depressed by this treatment (38, 41, 43). Methyl testosterone therapy provokes similar changes, but it is associated with an increased excretion of creatine (67).

The anabolic effects of testosterone have been utilized, with some success, in the treatment of Cushing's disease (1), Simmonds' disease (66, 68), and Addison's disease (39, 60). To a male and a female patient with Addison's disease, Kenyon and associates (39) administered 25 mg. of testosterone propionate daily for five days. They found that the response in the urinary constituents corresponded closely to that obtained in normal and hypogonad men and women. There was no alteration in the creatinine excretion in either case.

Talbot, Butler and MacLachlan (60) used testosterone therapy in an eight year old girl who had Addison's disease, moniliasis and idiopathic hypoparathyroidism. Methyl testosterone, in large doses (90 mg. daily), did not prevent the development of symptoms and signs of acute adrenal cortical insufficiency when desoxycorticosterone acetate was withdrawn. On the other hand, testosterone propionate in enormous doses, 50 mg. daily, "relieved the patient of all signs and symptoms of acute adrenal insufficiency after the discontinuation of desoxycorticosterone acetate therapy." With the testosterone treatment, used in conjunction with desoxycorticosterone and sodium chloride, there was a gain in body weight, a decrease in the urinary excretion of nitrogen, potassium and sodium, and a marked fall in the serum potassium concentration.

Werner and West (66) reported that "striking subjective, objective, and laboratory changes followed the treatment with methyl testosterone of four patients with Simmonds' disease. Clinically, the patients demonstrated renewed vigor, sense of strength and libido, and redeveloped secondary sex characteristics." There was nitrogen retention associated with a persistent weight gain. Marked creatinuria developed after a latent period of several weeks and subsided in about the same length of time after stopping treatment.

We have followed the response to various types of androgen therapy in 11 patients with adrenal insufficiency (*supra vide*), six with Simmonds' disease and five with Addison's disease. Seven of these patients have been observed frequently for from two to three years, while the others have been followed for only a few months. Nine of the patients have been treated by the implantation of testosterone pellets, each patient receiving from 150 to 450 mg. Three of the patients have had replenishments of these pellets. Six subjects were treated with methyl testosterone for ten days or longer. One man has had several courses of methyl testosterone therapy, each lasting one to two months with intervals of one to several months between treatments. Six patients were treated with intramuscular injections of testosterone for one to five weeks; 25 mg. was given at one to two days intervals. Three patients were treated with androstanediol, and two with methyl androstanediol. The above therapy was given to some patients who were well regulated concerning the salt and water metabolism, and to others who were only partially regulated. Opportunities were afforded to observe the response to treatment while patients were working and also to note the results during infections.

In all cases the testosterone therapy resulted in increased strength, energy and sense of well-being. These changes occurred whether the therapy was given orally, intramuscularly or by the subcutaneous implantation of pellets. However, there was a difference in the

clinical response exhibited by the patients with Simmonds' disease as compared with those with Addison's disease. In the former the changes were apparent within a few days and progressed to the point where the improvement was of marked degree in each case. The response in the patients with Addison's disease was slower and in no case was it of marked degree; it tended to be only slight or moderate. It is not clear as to why this difference should exist. Each group of patients seemed to have about the same degree of adrenal insufficiency, clinically and as evidenced by the special laboratory studies. The treatment was similar in the groups, except that three of the patients with Addison's disease were not treated with desiccated thyroid.

The testosterone therapy did not have the same effect on the urinary constituents in each patient. However, it usually caused a decreased excretion of sodium, chloride, potassium, and nitrogen. Methyl testosterone caused no increase in the excretion of 17-ketosteroids whereas testosterone propionate caused an increase; these findings are in accord with those of previous observers (12, 19, 44, 60, 66). There was a slight increase in the excretion of creatinine following the methyl testosterone therapy, which was not continued long enough to observe the marked creatinuria reported by others (66, 67).

The clinical response to androstanediol was similar to that of methyl testosterone but of less degree. In neither of the two cases in which metabolic studies were conducted did the androstanediol cause nitrogen retention; indeed, there was an increased excretion. In one case there was a marked increase in the excretion of 17-ketosteroids, but no change in the other case. Others (12, 17) have reported an increase in the excretion of 17-ketosteroids following the administration of androstanediol, but no increase after the administration of methyl androstanediol (17). Only slight improvement resulted in the two patients treated with methyl androstanediol. In one, no changes resulted in the urinary constituents; in the other, there was a slight retention of potassium, nitrogen, creatinine and creatine, but no change in the sodium, chloride or 17-ketosteroids.

With the continued observation of some of the above patients, one point becomes quite striking. After several weeks of therapy the water and electrolyte balance became well regulated, the patient gained weight and strength, and appeared capable of carrying on normal activity. However, within a short time after obtaining a job he would complain of the work being difficult and that he tired easily. Thus it appears that such individuals are lacking more in endurance than in "initial" strength. Although the muscle mass may be well developed, yet if there is a deficiency in the elements concerned in the repeated contractions of such muscles, fatigue and weakness will soon become apparent. In this connection the alterations in carbohydrate metabolism and the resulting effects on muscle performance may be considered.

In adrenalectomized animals or in patients with Addison's disease there is: (a) a marked decrease in liver glycogen (4, 48); (b) an increased carbohydrate utilization (13, 46, 63); (c) a decreased deaminization in kidney tissue (32, 53), a decreased rate of formation of carbohydrate from amino acids (45); a normal rate of deaminization (14, 45), in the liver and a normal rate of formation of carbohydrate from glutamic acid (45); (d) a decreased conversion in the liver of lactic acid (7), pyruvate or succinate (45, 63) to glycogen; a normal rate of conversion of succinic and pyruvic acid to carbohydrate in the kidney (53); (e) a decreased rate of oxidation of pyruvate and succinate by liver (64) and kidney (53) slices; and (f) a decreased muscle performance (23).

The alterations in carbohydrate metabolism may be corrected somewhat by therapy with salt, glucose or corticosterones. Adrenalectomized rats maintained in good health by the administration of sodium salts are said to show no abnormalities in the storage of carbohydrate (48). When, on the other hand, the adrenalectomized animal refuses food or when it is forced to fast, the liver glycogen declines to low levels, accompanied by less marked but significant declines in muscle glycogen and blood sugar values (47). Ingle (30)

showed that muscular weakness develops shortly after adrenalectomy and is not corrected by injections of salt. Injections of glucose produced an improvement in the work-capacity approximately equivalent to that obtained by the injection of cortical hormone (30). A close parallelism has been shown (25–29, 36) to exist between the state of carbohydrate metabolism and the capacity of muscle to respond to stimulation.

Glucose that has been fed can be transformed into liver glycogen at essentially a normal rate in adrenalectomized animals (2, 35, 48); the hormones of the adrenal cortex are not essential for the deposition of glycogen (2, 48), but they exert an augmenting effect. The hormones which affect the deposition of glycogen and gluconeogenesis also markedly increase the capacity of muscle to respond to continued stimulation (36); these compounds have an atom of oxygen on C_{11}.

In adrenalectomized animals the corticosterones cause: (a) an increased rate of storage of liver glycogen (4, 5, 6, 48), even in fasting animals; (b) an increase in urine nitrogen (48); (c) a decrease in carbohydrate oxidation (63); (d) a decrease in respiratory quotient (34, 63); (e) a decrease in glycogenolysis (11, 56); (f) an increase in the rate of conversion of keto acids to liver glycogen (45, 46); (g) an increase in blood sugar (5, 63); (h) an increase in the resistance to insulin (20, 21); and (i) an increase in the work-capacity of voluntary muscle (34).

In consideration of the problems involved in the patients with Simmonds' disease some of the alterations in carbohydrate metabolism in hypophysectomized animals are now presented. In hypophysectomized rats the administration of corticosterone and related compounds does not affect the glycogen in the muscle unless an extract of the anterior lobe of the pituitary gland is also given. There appears to be a synergism between the hormones of the adrenal cortex and those of the anterior lobe of the pituitary gland; either group alone is without effect on muscle glycogen (52). The depression of the oxidation of dextrose by corticosterone and related compounds is likewise dependent on the secretion of the anterior lobe of the pituitary gland. The administration of corticosterone and related compounds to hypophysectomized rats is without effect on the respiratory quotient unless an extract of the pituitary gland is also injected.

It is well known that the amount of glucose available in the body is important in muscular performance. In patients with Addison's disease the supply of glucose tends to be deficient; an adequate ingestion of salt and glucose aids in the storage of glucose, but corticosterone assures an adequate amount of glucose, provided that pituitary hormones are also available. In the treatment of the 11 patients with adrenal insufficiency, a special effort was made to furnish an adequate supply of glucose by the frequent ingestion of food. Corticosterone was administered only a few days and only in four patients. The prolonged use of corticosterones in the doses necessary is not practical at the present time, but when corticosterones with an oxygen atom on C_{11} are synthesized (36), this therapy will presumably produce very favorable results.

In the meantime the effects of stilbestrol on carbohydrate metabolism may be explored. Janes and Nelson (31) reported that diethylstilbestrol increased the liver glycogen of fasting rats and increased the excretion of nitrogen. The blood glucose and muscle glycogen were no different from those of the untreated normal animals. It is well known that estrogens, particularly diethystilbestrol, cause great enlargement of the adrenal cortex which in turn is dependent on the stimulation of the anterior pituitary. Long (47) observed that the effects of diethystilbestrol on carbohydrate and protein metabolism were due to its action through the pituitary on the adrenal cortex.

Stilbestrol dipalmitate was given for a few days to two patients with Addison's disease; each developed anorexia, nausea, and marked weakness. In neither case did the therapy increase the concentration of the blood glucose. Furthermore, insulin tolerance tests conducted before and after treatment in one case revealed no improvement.

SUMMARY

Studies of the effects of various hormones and allied substances were made in 11 patients with adrenal insufficiency; six had Simmonds' disease and five had Addison's disease. The main objective was to produce a clinical improvement superior to that obtained with desoxycorticosterone acetate alone, particularly with regard to the patient's muscular strength. Testosterone propionate, testosterone pellets, methyl testosterone, androstanediol, and methyl androstanediol improved the strength, their effectiveness decreasing in the order named. In Addison's disease, the myosthenic effect was slight to moderate, but in Simmonds' disease it tended to be more pronounced. However, particularly in Addison's disease after the patient had worked for a few hours he noticed fatigue definitely more than normal. The deficiency in the corticosterones is regarded as the probable cause for this fatigue. Stilbestrol dipalmitate, given intramuscularly to two patients with Addison's disease, produced marked weakness, anorexia and nausea.

Metabolic studies were conducted in four patients with Addison's disease and in two with Simmonds' disease. There was a slight variability in the response. Testosterone propionate, for the most part, caused a retention of sodium, chloride, potassium, nitrogen, creatine and creatinine, but an increase of 17-ketosteroids. Methyl testosterone caused a retention of sodium, potassium, nitrogen, an increased excretion of creatinine, and no change in the 17-ketosteroid excretion. Androstanediol, given in large doses (80 mg. daily) to one patient with Addison's disease, caused a slight retention of sodium and chloride, but an increased excretion of potassium, nitrogen and especially the 17-ketosteroids. Methyl androstanediol, given to two patients with Addison's disease, did not markedly affect the sodium, chloride, potassium, nitrogen, creatinine, creatine or 17-ketosteroid excretion.

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The Protein-Bound Plasma Iodine in Patients with Thyroid Disease[1]

II. The Effect of Thiouracil

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SINCE the demonstration by the Mackenzies (7) that thiourea causes a depression of thyroid activity in rats, the possibilities of this drug and its derivatives in the management of hyperthyroidism have received much attention. Astwood (1) first reported clinical improvement and a fall in the basal metabolic rate of patients treated with either thiourea or thiouracil. Thiourea, however, has been discarded by many workers in favor of the more active and less toxic thiouracil. Preliminary reports are now available from several sources which indicate that, although thiouracil has the ability to cause varied and severe reactions, its administration to hyperthyroid patients is followed almost invariably by considerable clinical improvement and decrease in the basal metabolic rate (1, 2, 4, 6, 8–10). Recently it has been shown that this drug also reverses the biochemical alterations of the thyrotoxic patient in a manner similar to the reversal produced by lugolization or thyroidectomy (9).

The mechanism of the action of thiouracil has not been clearly established. Since it does not abolish the activity of exogenous thyroxin (3) it is believed that the drug acts by inhibiting the synthesis of thyroxin in the thyroid gland. If this is the case, the protein-bound plasma iodine (hormonal iodine) may be expected to decrease parallel to the fall in metabolism.

MATERIALS AND METHODS

The plasma concentration of protein-bound iodine and the basal heat production were determined as described previously (5). These were performed on patients with hyperthyroidism who were being treated with thiouracil. The present report embraces 18 consecutive cases of toxic diffuse goiter in which the drug was used for periods ranging from eight days to four months. In thirteen cases, thiouracil was prescribed for from two to four months in order to determine its value in the medical management of hyperthyroidism; in four cases, it was employed only preoperatively; in one, the drug was withdrawn at the end of the third week because of neutropenia.

The thiouracil[3] in all cases was administered orally, usually 100 mg. tablets being given singly at intervals throughout the day. For most patients 100 mg. every six hours (400 mg. per day) was an adequate initial dose, although occasionally 100 mg. every four hours (600 mg. per day) was given. In five to eight days, this initial dose was reduced to 100 mg. every eight hours (300 mg.

[1] Aided by a grant from the Josiah Macy, Jr. Foundation.

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[3] We are grateful to Dr. B. W. Carey and to Dr. Stanton Hardy of the Lederle Laboratories for a generous supply of 100 mg. tablets of 2-thiouracil ("Deracil").

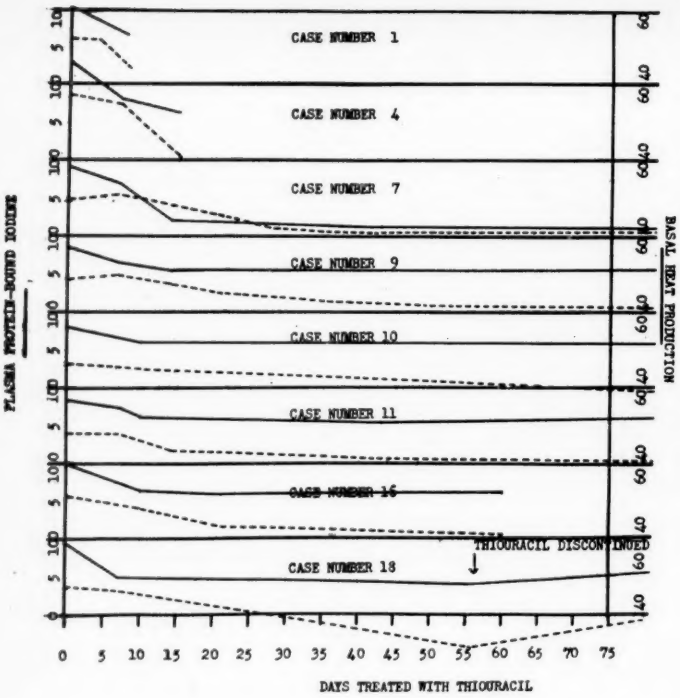
CASE NUMBER 1
CASE NUMBER 4
CASE NUMBER 7
CASE NUMBER 9
CASE NUMBER 10
CASE NUMBER 11
CASE NUMBER 16
CASE NUMBER 18
THIOURACIL DISCONTINUED
PLASMA PROTEIN-BOUND IODINE
BASAL HEAT PRODUCTION
DAYS TREATED WITH THIOURACIL
0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75

FIG. 1. The laboratory course of eight patients treated with thiouracil is illustrated in the above figure. The solid line represents the protein-bound plasma iodine in micrograms per 100 cc. of plasma and the dotted line shows the basal heat production in calories per square meter per hour.

TABLE I. THE EFFECTS OF THIOURACIL ON THE PROTEIN-BOUND IODINE, BASAL HEAT PRODUCTION AND PLASMA CHOLESTEROL IN 18 PATIENTS WITH TOXIC DIFFUSE GOITER

Case Number	Initial					Thiouracil Treatment			Final					Remarks
	Plasma iodine gamma %	Basal heat production cal/sq.M./hr calc.	Basal heat production cal/sq.M./hr det.	B.M.R. %	Plasma cholesterol mg. %	Initial dose mg./day	Days treated	Maintenance dose mg./day	Plasma iodine gamma %	Basal heat production cal/sq.M./hr calc.	Basal heat production cal/sq.M./hr det.	B.M.R. %	Plasma cholesterol mg. %	
1	10.5	52.7	52.5	+50	168	600	8	—	7.0	42.5	41.5	+18	184	Thyroidectomy on 9th day.
2	7.4	44.7	45.4	+22	177	400	10	—	6.0	39.9	40.0	0	236	Thyroidectomy on 10th day.
3	17.7	64.5	65.3	+62	90	400	12	—	7.0	42.5	43.1	+ 9	198	Thyroidectomy on 13th day.
4	12.8	57.0	56.1	+40	110	600	10	—	6.1	40.3	42.0	+ 5	190	Thyroidectomy on 11th day. Lugol's solution for 2 weeks before thiouracil failed to change B.M.R..
5	7.2	44.0	41.6	+16	160	600	24	—	5.3	37.9	37.0	+ 3	254	Thiouracil discontinued on 24th day on account of WBC 4050 (P 31%) on routine blood count.
6	11.6	55.6	55.4	+29	134	600	118	200	6.8	42.7	42.5	− 1	284	
7	9.1	49.3	49.9	+29	100	600	124	200	6.0	39.9	40.0	+ 4	202	
8	14.0	59.2	62.5	+63	120	600	122	200	6.7	42.5	42.2	+10	190	
9	8.4	47.5	48.5	+35	200	400	91	200	5.7	38.8	40.7	+14	192	
10	8.0	46.4	46.4	+25	215	400	96	200	5.7	38.8	38.0	+ 2	198	
11	8.3	47.7	48.1	+28	142	400	88	200	6.1	40.3	40.0	+ 6	156	Persistent tachycardia of 120/min. with palpitation on exertion. Had luetic heart disease.
12	7.8	45.8	45.3	+26	170	400	80	100	4.3	32.4	33.6	− 6	300	
13	9.0	49.2	54.1	+41	164	400	73	100	5.3	37.9	41.8	+ 9	326	Anxiety; still complains of palpitation and nervousness.
14	6.5	41.8	40.0	+21	146	400	69	100	4.9	35.3	35.1	+ 6	268	
15	11.0	53.8	53.5	+63	96	400	70	200	5.0	35.8	34.9	+ 8	200	This patient had a recurrence of symptoms of thyrotoxicosis on 50 mg. b.i.d. but was well on 100 mg. b.i.d.
16	10.0	51.5	51.5	+29	110	400	60	100	6.1	40.3	40.5	+ 1	288	
17	8.4	47.5	46.9	+22	—	400	60	100	5.6	38.3	38.5	0	—	
18	9.1	49.3	47.5	+22	188	400	56	100	4.0	30.7	30.4	−22	400	Early symptoms of hypothyroidism became evident.

per day) and within two weeks this was again decreased to 50 or 100 mg. every 12 hours (100–200 mg. per day). Urinalyses, blood counts and basal metabolisms were done at weekly intervals. Vitamin B complex, Lederle (3 capsules a day), and ascorbic acid (200 mg. a day) were prescribed simultaneously. Cases 7 through 18 also received 250 units of "folic acid" (grass juice concentrate)[4] per day.

When thiouracil was used preoperatively, thyroidectomy was performed 8 to 12 days after instituting treatment with the drug. On this regime, the basal metabolism was at or near normal levels at the time of operation. No severe technical difficulties (J.W.H.) were encountered during surgery.

RESULTS AND DISCUSSION

The results are summarized in the accompanying table and some representative cases are graphed in the figure. Within 4 to 7 days after the beginning of treatment, the protein-bound plasma iodine usually had begun to drop toward normal levels. In most cases, the iodine had reached the normal range within two weeks. The basal heat production fell more slowly, seldom declining within a week after the institution of treatment. However, by the end of the second week the basal heat production had also decreased to approximately normal levels. The basal heat production could be calculated from the plasma protein-bound iodine concentration using the equation $BHP = 52.3 \log (I) - 0.8$ calories per square meter per hour, previously shown to be accurate for patients with thyroid disease and after lugolization or thyroidectomy (5). This calculation yielded accurate results both before treatment and after the thiouracil had caused the blood iodine and the basal heat production to reach a steady state. The mathematical correlation, however, was inaccurate in the period during which the metabolic rate and the iodine concentration were declining. These results agree in a general way with those obtained by Williams and Bissel (10) who found a decline in the plasma iodine concentration of thiouracil treated patients. These workers, however, made no attempt to correlate the plasma iodine with the basal metabolic rate.

These results are entirely compatible with the assumption that thiouracil interferes with the synthesis of thyroxin. In this case, one would expect exactly what was found: the first detectable effect of the drug is a fall in the circulating thyroid hormone as measured by the protein-bound plasma iodine. Later, the basal heat production also declines as the thyroid hormone available to the body decreases.

It should be mentioned that no patient in this series showed any change in the size of the thyroid gland or in the degree of exophthalmos following thiouracil administration. As yet, thiouracil has not been discontinued in any of the long-term treated patients in order to see if persistent remission of the hyperthyroidism could be obtained as recently described by Astwood (2).

SUMMARY

Thiouracil (when administered to 18 patients with hyperthyroidism) caused a reduction in the basal heat production and in the protein-bound iodine of the plasma.

After these changes have been produced, the relationship previously demonstrated (5) between plasma iodine concentration and basal heat production was found to be entirely valid.

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Premature Sexual Precocity in a Young Girl

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PREMATURE sexual precocity is not rare. In the case reported here, daily gonadotropic, estrogenic, androgenic (17-ketosteroids) and progestin metabolic products (sodium pregnanediol complex) assays were made almost every day for 50 days. This child apparently was endocrinologically a normal adult female, but in age a child.

CASE FINDINGS

R.J., a girl 4 years and 11 months of age, was brought to the author's office because of precocious menstruation and abnormally rapid growth. She was born February 21, 1935, as shown by the birth certificate; delivery was normal. She weighed 9¾ pounds at birth and 17 pounds at two months.

The father of the patient was 32 years old, weighed 128 pounds and was 5 feet and 8 inches tall. The mother was 28 years old, weighed 173 pounds and was 5 feet and 5 inches tall. The mother's menstrual periods began at the age of 12 years. The patient had one sister, 10 years old, apparently normal.

The patient's weight was 72 pounds and her height was 4 feet and 5½ inches. The pulse rate was 104; heart sounds were normal. The respiration rate was 20 per minute; there were no râles. The circumference of the head at the brow was 22 inches; chest, 27.7 inches; abdomen at umbilicus, 26.1 inches; hip at trochanter, 20.1 inches; span, 57.6 inches; height, trochanter to floor, 30.1 inches; trochanter to top of head, 33.5 inches. Pelvic measurements were: anterior superior spine, 19.5 cm.; intercrestal, 23 cm.; external oblique (right and left), 19 cm.; transverse outlet, 8 cm.

The hair was short, and was dark brown in color. The eyes were normal. All of the deciduous teeth were present. The skull was rather large, the neck normal. The body was well developed generally. The breasts were large, measuring 6 cm. in diameter, and the fatty-glandular tissue was 3 to 4 cm. deep. The nipples were well developed, pink and inverted. The abdomen was normal except that its skin was somewhat scaly and showed some old scars from a skin infection (see Fig. 1).

The external genitalia showed a scanty growth of pubic hair. There was no axillary hair. The vaginal orifice admitted one finger with difficulty. There was no unusual development of the labia. The mucosa was similar to that of the normal adult (see fig. 2).

Rectal examination revealed an apparently normal cervix and uterus. The pH of the cervical secretion was 7.4 and of the vaginal secretion, 4.0. There was a questionable mass felt in the right adnexa, but none in the left. There was no menstrual flow at the time of the examination.

The mother stated that the baby's breasts were unusually large at birth. She noticed that the baby at two years of age was much larger than other children and also larger than her first child at this age. She seemed to be precocious mentally, although she liked to play with dolls and her attitude toward both boys and girls was the same as that of other children.

In the fall of 1938, when the child was four years old, the mother noticed that she had vaginal bleeding. This occurred again after an interval of 30 days, lasting only one day.

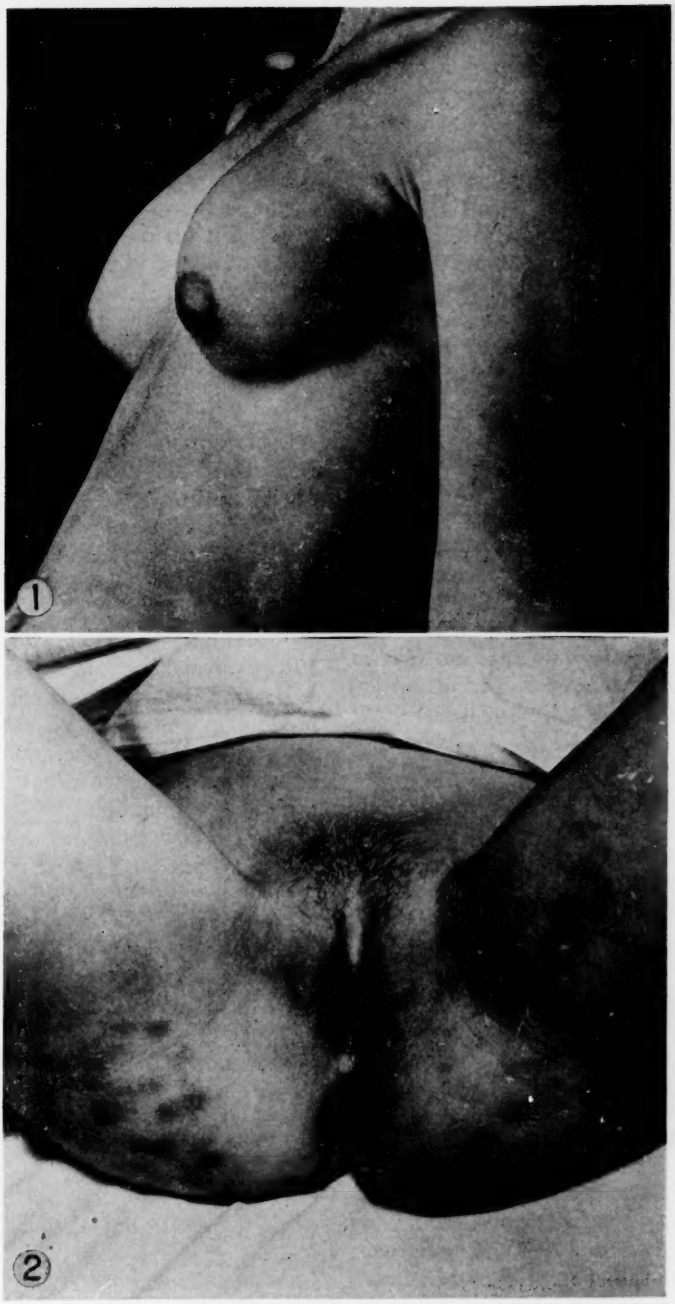

FIG. 1. The torso of patient *R.J.*
FIG. 2. The perineum of patient *R.J.*

On January 11, 1940, the patient began to have a profuse flow which lasted six days and was not accompanied by pain.

She was hospitalized on February 5, 1940. Examination showed the cardio-vascular and gastro-intestinal systems to be normal. The breasts were large and the body generally was well developed.

The findings of psychological tests made on February 9, 1940, were: chronological age, 5 years; Stanford-Binet mental age, 5 years; Stanford-Binet intelligence quotient, 100; Goodenough mental age, 5 years 9 months; Goodenough intelligence quotient, 115.

These findings yield a tentative rating of average intelligence. There is some suggestion that, with complete coöperation, the patient might have been able to rate some points higher. She succeeded at the six year level in some tests, such as the vocabulary test. The examiner estimated that a maximal rating on the patient, as to general intelligence, would be represented by an I.Q. of 109, indicating a classification of average intelligence. The quality of her responses does not suggest superior ability.

PROGRESS

The child remained in the pediatric ward for 83 days. Her only illness was an impetigo with a slight elevation of temperature.

A twenty-four hour urine specimen was collected, and pituitary and estrogenic hormones were determined by the author and also by Dr. W. K. Cuyler of Duke Hospital, Durham, N. C.

An exploratory laparotomy was performed by the author on March 26, 1940. Upon opening the abdomen it was seen that the ovaries, tubes, and uterus were adult in size and appearance. The uterus measured approximately 5.5 by 3 cm. and was pearly white in color. Both ovaries were sectioned lengthwise and throughout the stroma were many small yellowish bodies. Eight of these were removed. Also, a section of about $\frac{1}{8}$ of each ovary was removed for further study. A biopsy of the left breast was done by Dr. R. C. Patrick. She recovered from the operation uneventfully.

The child began to bleed exactly 48 hours after being operated upon and bled for 33 hours. Then, on June 8 she bled again for 12 hours. This was more of a spotting than a regular flow. During this flow the pH of the vaginal secretion was 7.3, and 12 hours after the flow stopped it was 4.5. The pH of the vaginal fluid was determined almost every day, and it varied from pH 3.8 to 4.6.

She was seen in the author's office at intervals of from six weeks to six months after dismissal from the hospital. The last visit was April 19, 1945.

ASSAYS

Urine specimens were received daily at Duke University from February 16, 1940 to April 5, 1940.

I. *Sodium Pregnanediol Complex* (progestin metabolic product): The total daily excretion before operation was 122 mg. The melting point was 240 degrees centigrade. The average total daily excretion after operation was 19 mg. (no melting point; 46 determinations).

II. *17-Ketosteroids* (androgenic metabolic products): The daily average value of 17-ketosteroids before operation was 29 I.U., and the daily average after operation was 18 I.U. (49 determinations).

III. *Urinary Estrogenic and Gonadotropic Values* (*per 24 hour period*):

Date	Estrogen Values Rat Units	Gonadotropin Values Rat Units
2-16-40	54	
2-17-40	46	
2-18-40		7.5
2-20-40	30	
2-21-40	30	
2-22-40		7.5
3- 3-40	38	
3- 4-40	12	
3-13-40	11	
3-14-40	15	
3-24-40		5.0
3-25-40	35	
3-26-40	49	
3-37-40	32	
3-28-40	14	
4- 2-40	5	
4- 3-40	9	
4- 4-40		5.0

In our own endocrine laboratory on February 6, 1940, the estrogen assay showed 24 rat units per 24 hours, and was negative for

pituitary gonadotropin. On February 9, 1940, the assay showed 20 rat units of estrogens, and again was negative for pituitary gonadotropin. Dr. A. E. Rakoff of Philadelphia found 3 to 6 mouse units of estrogen per 100 cc. of blood. The extraction of estrogen was performed in our laboratory by the method of Kurzrok (1).

ROENTGENOGRAPHIC STUDIES

Roentgenograms of the skull showed it to be characteristic of a child of about 12 years of age. The thymus was not enlarged; the bones of the hands and forearm had the appearance of those of a child about 10 years of age; the epiphyses of the knees and ankles showed the amount of union expected in a child of about 15 years of age; the teeth were those of a child of four years and eleven months; the skiodan technique revealed the uterus to be larger than normal. The tubes were patent. In the intravenous urogram the kidneys appeared normal in size, shape and position.

OTHER LABORATORY TESTS

The sedimentation rate was 18 mm. in one hour; the erythrocyte count was normal; the serum chloride, sugar, total non-protein nitrogen, creatinin, urea nitrogen, uric acid, and the glucose tolerance were all normal. The blood cholesterol was normal. The urine was normal.

SURGICAL PATHOLOGY

Endometrial biopsies were taken on February 7, 1940, September 6, 1940 and December 16, 1940. Two showed a normal proliferative stage of the endometrium and one was suggestive of secretory endometrium. A vaginal biopsy showed an adult type of mucosa.

Specimen Obtained at Operation, March 26, 1940. "Microscopic: (1) Sections of endometrium show small glands, the epithelium of which in a few places presents early proliferative changes. A few of the epithelial cells show vacuoles at the base and the nucleus is pushed toward the center of the gland. The stroma is dense and normal throughout. (2) Sections of right ovary show numerous immature nonripening ova lying in the usual ovarian fibromuscular tissue. I can find no evidence of ripening follicles and no corpora hemorrhagica or corpora lutea. Iron stains fail to reveal any evidence of pigment such as should be present. (3) Sections from the left ovary are similar to those on the right. (4) Section of left breast present small glands, a few of which are dilated and are lined by flattened glandular epithelium. The glands are lying in a heavy connective tissue matrix similar to that of the young breast before puberty, yet the glands are of a more adult type. There is no evidence of proliferation of the glandular epithelium such as a secretion of the breast would give, but I feel that there is sufficient evidence here to indicate that the breast is abnormal for a child of this age and is much more mature than one would expect. (5) Section of a small nodule found in the left broad ligament shows a thin capsule within which are multiple large cuboidal cells with vacuolated cytoplasm and large central nuclei which are deeply stained and round. These cells resemble the cortical cells of the adrenal gland and are evidently an adrenal rest. (6) Section of a cyst taken from the left Fallopian tube shows the lining to be composed of epithelioid cells, but in the opinion of the writer these are endothelial cells taking on the process of secretion. The wall is loose connective tissue and I believe this can be classified as a peritoneal inclusion cyst.

"*Diagnosis:* endometrium, partly in resting, partly in very early proliferative stage; normal ovary; adrenal rest; peritoneal inclusion cyst."

COMMENTS

A case of premature sexual precocity in a girl age 4 years and 11 months is presented with the data of numerous hormonal assays performed upon her urine and blood. There were 17 assays of estrogenic hormone, 7 of gonadotropin, 46 of the 17-ketosteroids (androgenic metabolic products. The values obtained were approximately those found in a normal adult woman.

The appearance of the vaginal mucosa and

the values of vaginal hydrogen ion concentration were those of an adult woman.

The ovaries, Fallopian tubes, uterus, cervix and vagina were also those of a normal adult female.

Both ovaries showed throughout many yellow bodies (believed to be adrenal rests) and similar bodies were scattered over the anterior and posterior peritoneal surfaces of the uterus and both broad ligaments. The pelvic peritoneum was studded here and there with these minute yellow raised areas. This case may represent an example of adrenal rests causing feminization instead of the usual masculinization, as described by Novak. Both Dr. Erickson of the Department of Pathology of Duke University and Dr. Donald Henderson of the Department of Pathology of Jefferson Davis Hospital diagnosed these yellow bodies as *adrenal rests*.

SUMMARY

The case is reported of a girl, aged four years and eleven months, who had approximately the genital development of an adult woman. The personality and intelligence were appropriate to the chronological age.

The urinary estrogen ranged between 5 and 54 rat units per 24 hours. Gonadotropin values varied from 5 to 7.5 rat units.

At operation numerous cell agglomerations were found within the ovary and studding the peritoneum. These upon microscopic study were diagnosed as adrenal rests.

The case apparently adds one more to the list of published instances of feminization from functioning adrenal rests in ovaries.

ACKNOWLEDGMENTS

The writer wishes to express appreciation to Dr. J. E. Hodges and Dr. Tom Kennerly for their kind assistance in this case. Thanks are also due Dr. E. C. Hamblen, Mr. Cuyler, Miss Baptist and Mrs. Ashley of Duke University for determining the titers on the 50 consecutive urines. The work of Dr. Donald Henderson, pathologist at the Jefferson Davis Hospital has been extremely helpful. The writer is greatly indebted to Mrs. Susie Kemp, in charge of the pediatric department, and to all the excellent nurses and internes who helped with this case. Of especial helpfulness were the pathological reports submitted by Dr. Erickson, Department of Pathology, Duke University.

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EDITORIALS

IMPROVED FORMS OF INSULIN

THE GREAT facts forever foremost in the minds of those who treat patients with diabetes are that insulin is easily available almost everywhere and that with its proper use death from diabetes need not occur and normal health and vigor are possible. The majority of students of the disease are agreed that the more nearly normal the blood glucose values are throughout the day, the greater are the chances to keep the diabetic patient in an optimal state of well-being. Regular insulin caused wide fluctuations in blood glucose levels and required multiple injections. Therefore, various slowly acting types of insulin were tried, and protamine-zinc insulin has emerged as the most widely used form for maintenance therapy. It was hoped that a single injection daily of protamine-zinc insulin would suffice to establish good control in the great majority of cases.

This hope has not been realized. Only the milder cases (usually those requiring forty units or less daily) can be well regulated with protamine-zinc insulin alone. The present market form of protamine-zinc insulin is entirely a precipitate which is slowly absorbed over a period of twenty-four hours or more. In mild cases, in which the rise in blood sugar after meals is not great, such an insulin may prevent hyperglycemia during the day as well as during the night. In severe cases, however, it is usually not possible to give enough protamine-zinc insulin to control the blood sugar rise after food intake without causing nocturnal hypoglycemia. Such hypoglycemia does not occur "because protamine-zinc insulin acts strongest at night," (an over-worked and inaccurate cliché), but because of the failure to take food at regular intervals during the night. If the patient ate regularly every four hours day and night protamine-zinc insulin, because of its slow, constant activity, should prove ideal.

For practical purposes a compromise or combined form of insulin therapy is often very satisfactory: two separate injections are given each morning, one of protamine zinc insulin (P.Z.I.) and one of regular insulin (R.I.). Usually the amount of P.Z.I. needed is about three times as large as the dose of R.I. required and the patients receive P.Z.I. forty-five units and R.I. fifteen units, or P.Z.I. sixty units and R.I. twenty units, etc. Although this is probably the best plan which is possible with the present market forms of insulin for patients with severe diabetes, it is far from ideal. Two injections daily are necessary, and patients often become confused with the two different types of insulin and two different sized doses.

Efforts to devise an insulin which, with a single injection daily, would establish good regulation in severe as well as mild cases have taken several directions: (1) proteins other than protamine, such as globin and histone, have been combined with insulin; (2) protamine-zinc insulin has been modified by varying its protamine and zinc content, and by changing the pH.

Histone-zinc insulin and globin-zinc insulin have been rather thoroughly studied. Neither of these modifications has given both the rapid effect and the prolonged activity desired. Modifications of protamine-zinc insulin containing only a half or a third as much protamine as market protamine-zinc insulin have given the most encouraging results. Two types of insulin with such lower protamine content have been suggested: (1) a biphasic insulin containing about twenty-five per cent of the hormone in quickly absorbable form, and seventy-five per cent in precipitated slowly absorbable form—this has been designated M.P.Z. insulin by MacBryde (4, 5); and (2) a monophasic insulin in which all of the hormone is precipitated. The precipitate, however, is saturated with insulin and there is no excess protamine, so that the hormone is more quickly released than from standard P.Z.I., which contains a large excess of unsaturated protamine. This is essentially the product obtained by mixing crystalline insulin with P.Z.I. in the proportion of 2:1, as suggested by Colwell (1).

There have been several comparative clinical studies of the suggested new insulins. Peck (6) obtained good results both with the modified protamine-zinc (M.P.Z.) insulin and with a 2:1

crystalline-P.Z.I. mixture, the comparative figures being somewhat better with the former. Del Fierro and Sevringhaus (2) established good control in fifteen of seventeen cases with M.P.Z. insulin and found it superior to P.Z.I., globin-zinc insulin or mixtures. MacBryde and Reiss (3) compared M.P.Z. insulin with the 2:1 mixture in a series of ten severe cases and reported better twenty-four hour blood sugar curves in every case with the M.P.Z. insulin; the control with M.P.Z. insulin excelled that obtainable with globin-zinc insulin in 17 of 20 cases.

At the present time evidence seems to indicate that protamine-zinc insulin, modified by a considerable reduction in its protamine content, will in one of its forms prove to be the preferable insulin for maintenance therapy. Whether the type which seems to give the best results clinically (M.P.Z. insulin, containing both rapidly absorbable and slowly absorbable components) will prove sufficiently stable remains to be demonstrated. It would seem logical that a biphasic insulin could best control both the hyperglycemia following meals and the constant glycogenolysis demanding a small but steady supply of insulin every hour of the day and night.

C. M. MacB.

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ON MENSTRUATION

From the point of view of pathology, menstruation is a disease. No other "normal" function, with the presumed exception of labor and delivery, involves edema, leucocytic infiltration, ischemia from arteriolar spasm, capillary and arterial rupture and sloughing of tissue. The menstrual discharge resembles the blood found after death from overwhelming shock or pregnancy toxemia. From the point of view of pathologic physiology, no other "normal" process except the termination of pregnancy involves such rapid and large shifts in water metabolism, in creatinine excretion and in serum diastase and changes in systemic vascular physiology slightly suggestive of shock. No other "normal" episode except the onset of lactation is accompanied by such a rapid and often striking, though fortunately usually short-lived, disturbance in personality. Furthermore, the skin eruptions, sore breasts, headaches, backaches, thigh-aches, cramps, nasal congestion, dizziness, chilly sensations, abdominal discomfort and change in activity of bowel and bladder all bespeak a pathological phenomenon.

The Greeks were indeed correct in associating hysteria with the uterus, for neither the menstrual molimina nor such marked evidence of disturbed physiology have been observed in its absence. Though objective information is scant, the subjective molimina are also mild or absent in patients with estrogen-induced flowing, cyclic bleeding from a proliferated endometrium or functional flowing from a proliferated endometrium.

According to available information, true post-ovulatory menstruation is a widespread shedding of the endometrium; whereas bleeding from an estrogen-stimulated, proliferative endometrium is focal, there being far less breakdown of tissue. The debris of secretory endometrium, separated from the menstrual discharge, has been found extremely toxic (1). Late secretory, premenstrual endometrium, fresh from the operating room, ground and injected in saline suspension into immature rats has been found toxic. (2). Proliferative endometrium, even with hyperplasia, is not toxic. Thus it appears that the regression of a secretory endometrium is accompanied by a meta-

bolic change which yields a toxin. This toxin is the likely final cause of menstruation through vascular corrosion. It is suggested that menstruation and shock have much in common, both locally and systemically. Spontaneous debridement relieves the menstrual toxemia just as surgical debridement ameliorates that of traumatic shock.

The above considerations indicate that, in addition to the hormonal component involved in the menstrual phenomenon, there is another component, related to the change in endometrial metabolism. What other purpose can this other component serve besides relieving the uterus of a tissue unrequited by the receipt of a fertilized ovum, since there are systemic as well as local reactions to it?

The urinary FSH is increased just before or at the start of menstruation. The premenstrual engorgement of the breasts may be interpreted as reflecting pituitary lactogenic activity. The drop in serum diastase at this time can be thought of as evidence of increased adrenocortical activity, thus intimating a rise in the output of adrenocorticotrophic hormone. The premenstrual retention of water invites the idea that stimulation of the posterior lobe has occurred.

It seems hardly possible that these suggested evidences of menstrual hypophyseal activity could be due to nothing more than regression of the corpus luteum. The very fact that normal corpora lutea have been observed in patients whose wombs have been removed and in whom molimina are absent confirms this conclusion. Furthermore, any cyclic pituitary-ovarian interaction in these patients has not yet been shown. Actually, patients with a tiny amount of endometrium left after supracervical hysterectomy are likely to have "aperiodic" staining.

Can it be that the toxemia of menstruation, resulting from the regression and disintegration of secretory endometrium, is in primates a necessary supplement to regression of the corpus luteum for adequate cyclic hypophyseal stimulation? If, so, the induction of cyclic post-ovulatory-like bleeding is to be recommended for patients with functional disturbances, *viz.*, amenorrhea, abnormal bleeding and irregular cycles, in which "normal" (*sic*) hypophyseal stimulation is desirable.

On the basis of the above considerations, it would seem desirable, even urgent, to have available ampules containing 10, 15, 20 and 25 milligrams of progesterone, at a cost that would not unduly restrict their use.

GEORGE V. SMITH

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ASSOCIATION NOTICE

The Association for the Study of Internal Secretions has just announced that the award furnished by E. R. Squibb and Sons has been given to Dr. E. C. Kendall and that the award furnished by Ciba Pharmaceutical Products Inc. has been given to Dr. Jane Anne Russell (Mrs. A. E. Wilhelmi).

The Squibb Award to Dr. Kendall, was based on his fundamental contributions to endocrinology, in particular the isolation of thyroxine from the thyroid gland and his recent observations on the fractionation and functions of active principles of the adrenal cortex. Dr. Kendall is professor of biochemistry in the Graduate School, Mayo Foundation, University of Minnesota. He received the degree of Bachelor of Science from Columbia University in 1908 and the degree of Doctor of Philosophy from the same institution in 1910. He then held various fellowships until he became affiliated with the Mayo Clinic in 1914. He was given the honorary degree of Doctor of Science by the University of Cincinnati in 1923, and was president of the Association for the Study of Internal Secretions in 1930.

The Ciba Award was made to Dr. Russell because of her fundamental observations on the rôle of the anterior pituitary, adrenal and thyroid glands in the absorption and utilization of sugars and starches. Dr. Russell is an instructor in physiological chemistry at Yale University School of Medicine. She received the degree of Bachelor of Arts from the University of California in 1932 and the degree of Doctor of Philosophy from the same institution in 1937. She has held various fellowships, the most important of which are the Porter Fellowship of the American Physiological Society, a National Research Council fellowship in medicine and the Sterling Fellowship in the Department of Physiological Chemistry at Yale University.

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* F. A. DE LA BALZE, ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNA FORBES, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, JANET W. MCARTHUR, THOMAS H. MCGAVACK, J. R. REFORZO-MEMBRIVES, A. E. MEYER, DORIS PHELPS, E. C. REIFENSTEIN, JR., RUTH ST. JOHN, HAROLD WOOSTER, AND J. ZANARTU.

ENDOCRINE GENERAL

GRAU TRIANA, JUAN, D. ARGUELLES CASSALS, O. ROMERO JORDAN AND A. BULLE MERRY

Xanthoma diabeticorum and gigantism-acromegalia syndrome. *Vida nueva* 53, 274. 1944.

Report of a case of xanthoma diabeticorum in a white girl, fifteen years of age, presenting also manifestations of diabetes mellitus and a gigantism-acromegalia syndrome. The xanthoma was considered a secondary manifestation of the hyperlipemia, which in turn is a complication of diabetes.

The case is interesting for the following reasons: Xanthoma diabeticorum is a rare disease (131 cases in the literature, in 1941). Xanthoma diabeticorum is rare in women. For each female case there are seven male cases. The association of the gigantism-acromegalia syndrome gives great importance to the pituitary factor in the etio-pathogenesis of the disease.

The evolution of the case (the skin lesions were cured with a fat-free diet and injections of insulin) is characteristic of the disease and serves to confirm the diagnosis in an evident manner.—*Courtesy Diabetes Abstracts.*

HADDOW, A., J. M. WATKINSON, E. PATERSON, AND P. C. KOLLER

Influence of synthetic estrogens upon advanced malignant disease. *Brit. Med. J.* 2: 393. Sept. 23, 1944.

Seventy-three cases of advanced cancer received treatment with the synthetic estrogens triphenylchlorethylene, triphenylmethylethylene, or stilbestrol. Of 22 cases of late malignant disease of the breast treated with triphenylchlorethylene (usually in doses of 3 to 6 gm. per day over a period of several months), 10 showed a significant although temporary retardation, or even partial regression, of the tumor. No evidence was obtained to suggest that the drug will prevent the development of metastases. The initial effect of treatment in these cases passed off comparatively rapidly, and only one has shown prolonged arrest, the ultimate course of the disease being in no way altered in the remainder. The degree of retardation was less than could be expected from local palliative x-irradiation. Of 30 cases of advanced malignant disease other than cancer of the breast (including carcinomata of the skin, maxillary antrum, urinary bladder, ovary, rectum, and testis with reticuloendothelial growths and leukemia), and similarly treated with triphenylmethylethylene, only 2 (carcinoma of the bladder, carcinoma of the prostate) showed undoubted partial regression of the tumor. Of 14 cases of carcinoma of the breast treated with stilbestrol (average of 300–600 mg. by intramuscular injection or by mouth over a period of several months), 5 showed alterations in the growth and behavior of the tumor similar in nature to those produced by triphenylchlorethylene. Serial biopsies in a few cases with a marked clinical response showed histological alterations (diminution of mitosis rate, variations of staining behavior, and necrotic changes) of a type not resembling the changes following x-irradiation. The secondary signs of drug action included nausea, pigmentation of the mammary areola, mastitis in the male, uterine bleeding, and edema of the lower extremities. One or more of such changes occurred with special frequency in cases showing some degree of tumor regression. Several of these cases also manifested improved appetite, gain in weight, and diminution of pain.—*R.B.G.*

HERTIG, A. T., AND R. G. LIVINGSTONE

Spontaneous, threatened and habitual abortion: their pathogenesis and treatment. *New Eng. Med. J.* 230: 797. June 29, 1944.

Threatened abortion occurs in at least 16 per cent of all pregnancies. Spontaneous abortion

occurs in approximately 10 per cent of all pregnancies. Approximately 40 per cent of threatened abortions do not abort regardless of the treatment employed. Approximately 60 per cent of threatened abortions abort if untreated. On the basis of a series of 1000 cases examined embryologically and pathologically, approximately one-third of spontaneous abortions are theoretically capable of being salvaged at the time the patient is first seen by the physician. In view of the three preceding conclusion, approximately 60 per cent of threatened abortions under adequate treatment may fail to abort. Threatened abortion should be treated by some potent corpus luteum preparation or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C and K and thyroid, in conjunction with a program of so-called "nutritional adequacy." Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to or coincident with conception.—*R.B.G.*

JACOBSON, P.

The psycho-endocrine origin and therapy of recurrent spontaneous hemorrhage. *Virginia Med. Monthly* 72: 73. 1945.

Estrogen by injection produced hemostasis in 49 patients with various types of hemorrhage, as epistaxis, from gastric ulcer, tonsillar fossae, or in idiopathic hematuria. Doses of 2000 to 5000 units were administered to children and adolescents, and 10,000 units to adults. Epistasis occurred in from one-half to three hours. The author believes that patients with spontaneous hemorrhage suffer from emotional hypertension, and estrogen may serve to affect the mental condition, rather than by acting directly as a hemostatic.—*Courtesy R. J. Main.*

MEAKER, S. R., C. H. LAWRENCE, AND S. N. VOSE

Practical details in the management of sterility, with special reference to endocrine factors. *New Eng. Med. J.* 230: 755. June 22, 1944.

Certain abnormal conditions recognizable as obstacles to human fertility are discussed. These include constitutional depressions as well as disorders of the reproductive organs. In the typical clinical case of involuntary sterility several of these factors may be present, and they are usually divided between the husband and the wife. This paper discusses the methods of complete diagnostic study prerequisite to any well organized plan of treatment.—*R.B.G.*

PRESCOTT, F., AND M. BASDEN

Inhibition of lactation by hexestrol dipropionate. *Brit. Med. J.* 2: 428. Sept. 30, 1944.

A single intramuscular injection of 12.5 mg. of hexestrol dipropionate inhibited lactation in 66 per cent of a series of 44 mothers shortly after childbirth. When given within the first three days of delivery lactation did not occur, and there were no signs of breast engorgement or discomfort. Of the remaining 34 per cent all but 2 per cent ultimately responded to repeated injections. Only 18 per cent required treatment for more than three days. A further course of injections, given to suppress "secondary filling," was necessary in only 7 per cent of the cases. This compares well with the figure of 25 to 45 per cent for stilbestrol. Hexestrol dipropionate, given intramuscularly in one or two doses, was effective in suppressing lactation in five cases in which it had already been established. Hexestrol dipropionate given by mouth is not so satisfactory as when given by injection.—*R.B.G.*

RAMOS, PERALTA A.

Membranous dysmenorrhea as a factor in sterility. *Obst. y Ginec. Latino Am.* 1: 117. 1943.

The author presents a review of membranous dysmenorrhea. He states that the maximum pain is experienced in association with the highest estrogen and lowest progesterone levels. Three patients were treated with anterior pituitary extract alone or with this and progesterone intermenstrually and chorionic gonadotropin during the period. They all experienced relief of pain and became pregnant.—*J.Z.*

REPORT OF ROYAL SOCIETY OF MEDICINE

Stilbestrol for advanced breast cancer. *Brit. Med. J.* 2: 20. July 1, 1944.

The treatment by stilbestrol of nearly 100 cases of advanced carcinoma of the breast was discussed by several speakers at a meeting of the Section of Radiology, Royal Society of

Medicine. In the whole series recorded by the various speakers there were 69 patients under the age of 58; of these 43 had not improved, and none showed spectacular improvement. Of the 52 patients over 58, at least 17 had improved, and 6 or 7 were reported as showing spectacular improvement amounting in some cases to a complete disappearance of fairly advanced disease. What had been presented was regarded only as a preliminary experiment to determine whether the investigation was worth pursuing.—*R.B.G.*

RIOS, JOSÉ O., AND JOSÉ PENHA GODOY D'ALEMBERT

The influence of menstruation on the incidence of epileptic attacks. *Arq. Assistencia Psicopatas S. Paulo* 7: 449, 1942.

In 104 cases studied it was found that 57.7% experienced an increase in seizures during menstruation, which was in most cases compensated by decreases in the pre- and post-menstrual time. The influence of menstruation is most marked at the age from 26 to 30 years. It is most noted in the severe cases having a high incident of attacks, and in quiet and poorly nourished patients.—*A.E.M.*

SHAPIRO, H. A., AND H. ZWARENSTEIN

Correspondence—The use of the South African frog pregnancy test. *Am. J. Obst. and Gynec.* 48: 740. 1944.

The authors point out that the original report concerning this technique was published by them in October, 1933, in the Proceedings of the Royal Society of South Africa.—*E.C.H.*

WOLMAN, I. J.

Urine analysis in pediatrics; ten years' progress. *Am. J. Med. Sci.* 208: 767. 1944.

This review surveys the advancements in urinalysis which are of importance in the medical management of pediatric patients. Sections are devoted to: proteinuria; sediment counts (Addis); melituria (including a discussion of: a) techniques for recognition and identification, b) alimentary melituria, c) renal glycosuria, d) lead poisoning, e) intermittent glycosuria, f) diabetes mellitus, g) essential pentosuria, h) fructosuria, i) galactosuria, j) sucrosuria, k) glycogen storage disease (Von Gierke), and l) the Fanconi syndrome. Also discussed are the sulfonamides, pigments, and the findings in newborn and premature infants. There is a section on miscellaneous items including a discussion of: a) acetone, b) amylase, c) calcium, d) chlorides, e) cystine, f) indican, g) phenylpyruvic oligophrenia, h) 17-ketosteroids, and i) tyrosine and phenylalanine.—*E.C.R., Jr.*

HYPOPHYSES

HEMPKILL, R. E., AND MAX REISS

Pituitary cachexia treated with corticotrophic hormone. *Brit. Med. J.* 2: 211. Aug. 12, 1944.

A case of clinical pituitary cachexia in a nulliparous woman is described. Clinical and hormone studies indicated extreme hypopituitarism. Treatment with corticotrophic hormone resulted in complete restoration of weight and cosmetic features. The authors did not believe this case to be one of anorexia neurosa. The authors suggested that in this type of case there was a sudden functional reduction in pituitary activity later followed by the physical symptoms of hypopituitarism. The suggestion was made that the picture of pituitary cachexia without structural changes in the pituitary itself may follow the menopause.—*R.B.G.*

PANCREAS

BANYAI, A. L., AND A. V. CADDEN

Diabetes and tuberculosis. *Arch. Int. Med.* 74: 445. 1944.

An analysis of the reports of ten American clinicians based on the observations of 17,358 cases of diabetes indicates a higher incidence of tuberculosis in diabetic persons than in the general population of the United States. It is reasonable to believe that the increased susceptibility of diabetic patients to tuberculosis is due to a complexity of causes. On the basis of available clinical and experimental data we are of the opinion that hypovitaminosis A may have a significant rôle in this respect. The fact that an unusually high percentage of diabetic patients who acquire tuberculosis are not adequately treated for their pulmonary disease before it reaches the far advanced stage calls for an urgent revision of the diagnostic approach to this problem. For the recognition of early tuberculosis it is necessary to anticipate this disease. All diabetic patients should be tested with tuberculin and the test should be repeated periodi-

cally on all patients with negative reactions to tuberculin. A roentgenogram of the chest should be taken for all patients with positive reactions at least once a year. Adequate search for tubercle bacilli should be carried out when sputum is available or when roentgenologic observations justify repeated aspirations of the fasting gastric contents. In tuberculosis diabetic patients who were given a well planned diet and adequate amounts of insulin slight glycosuria and hyperglycemia not exceeding 200 mg. per 100 cubic centimeters are compatible with favorable therapeutic response as far as pulmonary tuberculosis is concerned. The results in this group of patients compare favorably with those recorded for tuberculous patients whose blood sugar was maintained on practically a normal level.—*I.B.*

BELLOWS, J. G.

The crystalline lens in diabetes mellitus. *Arch. Ophthalmol.* 32: 498. 1944.

Disturbances of the eye in diabetic patients are extremely common. The lens and the retina are most frequently affected. Two types of abnormalities of the lens appear: (1) transitory refractive changes and (2) diabetic cataract. The transitory changes are equally distributed throughout all age groups. Occurring only in cases of fresh diabetes with a high level of blood sugar and with glycosuria, diabetic myopia is less common and less in degree than diabetic hyperopia. The hyperopia always follows the myopia before a return to a normal refractive state can occur. Hyperopia, on the other hand, may arise without a preceding myopia. Most authors attribute the opacity to an osmotic or a toxic action of the excessive dextrose and its metabolic products.—*Author's Summary.*

BLOTNER, H.

Effect of prolonged physical inactivity on tolerance of sugar. *Arch. Int. Med.* 75: 39. 1945.

A study was made of the effect of prolonged physical inactivity on the dextrose tolerance of 86 nondiabetic patients—70 adults and 16 children—who had been confined to bed for from one month to 13 years by various pathologic conditions. A comparison was made between the dextrose tolerance of these patients and that of active adults and children. In general the sugar tolerance was diminished in the patients who had been confined to bed. The fasting blood sugar ranged from 70 to 130 mg. per 100 cubic centimeters, and the fasting urine was free from sugar. After the ingestion of dextrose the concentration of blood sugar rose to abnormal levels, the maximum being 364 mg., and varying amounts of sugar were found in the urine at various times. In many of the adults there was a high renal threshold for dextrose. In patients who later became ambulatory for several months the sugar tolerance returned to normal. Hypertension, vascular disease, obesity and infection in themselves did not appear to be significant as causes. The arteriovenous differences in the blood sugar of a group of inactive persons after the ingestion of dextrose ranged from 15 to 50 mg. per 100 cubic centimeters, which is normal or greater than normal. These results indicate that the muscles of the physically inactive patients are capable of utilizing sugar normally. It is suggested that during prolonged physical inactivity the pancreas is at rest because in this state there is not the demand for rapid storage and utilization of sugar that there is in active persons. Consequently, there may ensue diabetic-like reactions to dextrose tolerance tests even with normal fasting levels of blood sugar. —*Author's Summary*—*I.B.*

BRUNSCHWIG, A., AND J. G. ALLEN

Specific injurious action of alloxan upon pancreatic islet cells and convoluted tubules of the kidney. Comparative study in the rabbit, dog, and man. *Cancer Research* 4: 45. 1944.

Alloxan, the ureide of mesoxalic acid, when injected intravenously, produced specific necrosis of islet cells in the pancreas and epithelium of the convoluted tubules of the kidneys in rabbits.

In dogs, intravenous injection of alloxan also injured specifically the islets cells and convoluted tubules of the kidney. The islet cells in these animals, however, did not exhibit the extensive coagulation necrosis observed in the rabbits.

In dogs, 200 to 500 mg. of alloxan per kg. were fatal in from 1 hour to 6 days, the animals having died with definitely elevated blood glucose and blood N.P.N. After total doses of 100 to 150 mg. per kg., the animals sometimes survived with transitory diabetes and with or without transitory, impaired renal function. In one dog a sustained diabetes mellitus (over 28 days)

without elevated blood N.P.N. was observed.

Four human patients with carcinomatosis, one presenting an insulin-producing islet cell carcinoma of the pancreas, received intravenous injections of alloxan. Transitory, beneficial effects were observed in the patient with insulin-producing islet cell carcinoma, following injection of from 0.6 gm. to 1 gm. per kg., in that attacks of hyperinsulinism were abolished for ten to twenty days following each series of injections, whereas before the injections he had had two to five severe attacks a day. In the other three patients also, comparably larger doses of alloxan were given than in the dogs and rabbits, with effects on the blood sugar in only one instance. Hence it appears that the human subject is much more resistant to the action of alloxan than is the dog or the rabbit.—*Courtesy Diabetes Abstracts.*

EATON, JAMES C.

Clinical trial of globin insulin and other insulins with delayed action. *Lancet* 2: 269. 1944.

After these trials with globin insulin began two years ago, Colwell, Izzo, and Stryker (1942) reported that by mixing protamine zinc insulin with equal or larger proportions of soluble insulin all variations between the actions of protamine zinc insulin and insulin could be obtained. These proportions of insulin are much greater than have been used by most physicians. Because protamine zinc insulin normally contains an excess of protamine, the use of less than 50 per cent of insulin results in the mixtures' acting like pure protamine zinc insulin. Such results obviously have a bearing on the value of globin insulin. It was therefore decided to compare the action of globin insulin with such mixtures, as well as with protamine zinc insulin alone. Globin insulin was tested in forty-one cases of diabetes mellitus. In ten cases the blood sugar was followed for twenty-four hours and the results compared with those obtained using protamine zinc insulin alone or combined with soluble insulin. With mixtures of protamine zinc insulin and insulin, the uniformity of the blood sugar throughout the twenty-four hours was even better than with globin insulin, hyperglycemia being well controlled with nocturnal hypoglycemia. The early sharp fall in blood sugar usually seen when soluble insulin is given alone was absent, and there seems no doubt that such mixtures do not show the independent action of each type of insulin.—*Courtesy Diabetes Abstracts.*

ENGELHARDT, H. T., AND V. J. DERBES

Some observations on the treatment of uncomplicated diabetes. *Bull. Tulane M. Faculty* 3: 48. 1944.

For a number of years protamine zinc insulin has been used to regulate all diabetic patients in the Charity Hospital Clinic. With those patients who cannot be controlled with protamine zinc insulin alone, mixtures of unmodified insulin and protamine zinc insulin are used, beginning with 3.2 parts, respectively. The patient tests his urine before breakfast and before the evening meal. Results of the former test reflect primarily the effect of the protamine zinc insulin component of the mixture, and the before-supper sample indicates the action of the more soluble component.—*Courtesy Diabetes Abstracts.*

GASPAR, J. L.

Diabetes mellitus and pregnancy. *West. J. Surg.* 53: 21. 1945.

A review was conducted of 49 deliveries in 45 pregnant diabetic patients seen at the Los Angeles County General Hospital between 1935 and 1944. There were 19 stillbirths and 6 neonatal deaths, or a fetal mortality of 51%. A high percentage of stillborn infants was found from one to nine years before the clinical recognition of diabetes mellitus. It is suggested that glucose tolerance tests be performed on patients having unexplained stillbirths. In the majority of cases known to have diabetes before pregnancy it was found necessary following conception either to treat the patient with insulin or to increase the insulin in order to control the diabetic state. Diabetic complications while the patient was in labor and during the postpartum period were uncommon. Pre-eclampsia was found to be present in one third of the patients. No eclampsia was reported.—*J.M.*

GUIDOTTI, F. P., AND J. H. WINER

The rapid detection of sugar in urine. *Mil. Surgeon* 94: 111. 1944.

To determine the accuracy of this test, comparative series of 15,000 urine specimens were studied using both bismuth powder (galatest) and Benedict's test simultaneously.

The powder test showed itself to be reliable in elimination of the "negatives." This spot method was positive in every instance in which the Benedict's test showed the presence of sugar. The powder does not give a satisfactory quantitative estimation of the amount of sugar; therefore, Benedict's test is necessary for rechecks, which are performed routinely in all instances in which sugar is found.

Technicians should be examined for color blindness, since, in a severe degree, it will impair the ability to read the test.—*Courtesy Diabetes Abstracts.*

JORDAN, W. R.

Diabetic coma. *Virginia M. Monthly*, 71: 473. 1944.

Instruction of the patient in the importance of routine visits to the doctor and in prompt attention to any intercurring disease or upset in the diabetes should lessen the incidence of diabetic coma and improve the results of treatment. Death from diabetic coma may occur so quickly that the major part of the treatment should be given within the first two or three hours in order to obtain the effects of this treatment. Any delay in treatment can prolong the acidosis and the danger therefrom. Frequent clinical and laboratory observations help to prevent relapses and hasten convalescence. Emphasis should be placed on large doses of insulin. Second in importance is the administration of large amounts of saline solution intravenously. Profound coma, a sweating skin, low or absent blood pressure, anuria, and a CO_2 level of less than 12 volumes per cent indicate a grave prognosis and the need for insulin and intravenous fluids in much larger amounts than are customarily used. During the period of convalescence, the low resistance of the patient to disease must be remembered, and general care should be emphasized.—*Courtesy Diabetes Abstracts.*

LIEBERMAN, A. A.

Nervous and mental manifestations observed in spontaneous hypoglycemia. *Illinois Med. J.* 85: 287. 1944.

This paper discusses a case of spontaneous hypoglycemia due to pancreatic adenoma. Over a period of three years, the patient exhibited a progressive disturbance in conscious awareness and developed the characteristic ataxia, disorientation, seizures and mental deterioration due to proanoxia. Neurologic inventory suggested the diagnosis of taboparesis, but glucose tolerance studies paved the way for subsequent surgical extirpation of a pancreatic islet adenoma, followed abruptly by recovery in the psychiatric and neurologic areas. In the preoperative phase, improvement with glucose and adrenalin administrations was only transitory, quickly followed by relapse into hypoglycemic coma through a stimulated over-production of endogenous insulin. The patient has remained well 33 months post-operatively, a fact that emphasizes the remarkable reversibility of cerebral reactions in chronic hypoglycemia. Two additional cases are presented of "functional" hypoglycemia with amelioration of symptoms employing the high protein, moderate fat and low carbohydrate diet. Hypoglycemic states may manifest themselves as simulating any and all varieties of nervous and mental disorders. It is suggested that glucose tolerance studies be performed in all cases in which fluctuations in the level of conscious awareness are apparent.—*Author's Abstract.*

MARBLE, ALEXANDER

The successful treatment of diabetes. *Texas State J. Med.* 40: 231. 1944.

Despite the relatively high degree of dissemination of medical knowledge in this country, a disappointingly small percentage of diabetic patients receive insulin. From closely observed groups, it is known that 75 to 80 per cent of patients will benefit from its use. All too often the doctor follows the request of the patient to avoid insulin if at all possible, whereas, actually a much better policy is to give insulin to every diabetic patient unless some good reason exists for not doing so.

In recent years various types of insulins have been used in an attempt to secure one superior to protamine zinc insulin. One goal has been to prepare a type which would provide both a slow and a rapid action. These insulins, which have included histone zinc insulin and globin (zinc) insulin, have been used for a number of years experimentally with sizable groups of patients; globin (zinc) insulin has recently been offered for sale on the open market. The advantages of these newer types of insulin over protamine zinc insulin are not impressive.

The fact is that by varying the amount of modifying substance such as protamine, histone, or globin and by varying the content of zinc and the pH, one can produce an almost un-

limited number of modifications of insulin with correspondingly different rates and durations of action. Satisfactory control of the condition of most diabetic patients can be obtained with any of the insulins named above. However, in keeping with the principles outlined earlier, the aim should be to make the treatment of diabetes as simple as possible. Consequently, it would seem desirable to limit the number of insulins released for public sale to a minimum, and actually at the present time that would appear to be only two—some form of rapid-acting insulin and some form of slow-acting insulin.—*Courtesy Diabetes Abstracts.*

MURPHY, F. D.

Comments on treatment: Insulin. *Wisconsin M. J.* 43: 625. 1944.

The objection to globin zinc insulin is that diabetics vary in their requirements of slow-acting and rapid-acting components. The ratios of protamine zinc insulin to unmodified insulin vary considerably in different diabetics. Some diabetics progress satisfactorily when the ratio of modified insulin to unmodified insulin is 1:2. Others do better when it is 1:3 or 1:4 or 2:3. The disadvantage of the combinations already made up is that, while they are adequate for some diabetics, there are other diabetics who progress better on another combination of the same components.

Concerning the multiple forms of modified insulin being recommended, it would be a distinct step forward and would tend to simplify administration of insulin if the number were reduced to three. For practical purposes, there is need of a slow-acting insulin, such as protamine zinc insulin, and of a rapid-acting insulin, such as regular unmodified insulin. There is, in addition, room for one other which would combine their benefits and advantages and would eliminate, as far as possible, their disadvantages.—*Courtesy Diabetes Abstracts.*

OWENS, L. B.

The treatment of diabetic coma. *Cincinnati J. Med.* 25: 286. 1944.

The term "diabetic coma" has been rather loosely applied to the whole ketosis process, without regard to mental symptoms. The ketosis process is one of abnormal fat metabolism and is better described simply as acidosis or ketosis. The term "diabetic coma" should be used only with those patients in ketosis whose mental state has become one of complete unconsciousness. At the Cincinnati General Hospital, the mortality for all degrees of ketosis is 47 per cent. Over 50 per cent of the cases had been in ketosis over sixteen hours and were completely unconscious. The mortality of this group, which we have called diabetic coma, is slightly less than 75 per cent.

A careful study of the case records revealed that the most important factor associated with a high mortality was the duration of the ketosis before active treatment was instituted.

Early diagnosis and the prompt institution of adequate treatment should take first place. Of all the measures known in combating ketosis none can take precedence over these. Early and adequate treatment consists of many things. The first and most important is insulin. The second and equally important part of treatment is fluids. These will amount to 4000 to 5000 cc. in eight to twelve hours. An occasional case is found in which the ketosis is controlled but in which the carbon-dioxide combining power of the blood does not rise. Soda may be used to advantage in this type of case.

The use of glucose intravenously in the early treatment is not thought necessary. There has been much discussion on this subject. Various clinics in the country disagree as to its need. Some writers believe it does definite harm. In these studies, it has been shown that its use prolongs the recovery time, requires more insulin, and that in a comparison of mortality, there is little difference in those receiving glucose early and those not receiving it at all. Anuria is probably a part of the picture of shock. The greatest hope lies in the prevention of its occurrence by preventing shock or circulatory collapse. The one place left for improvement in the handling of diabetic coma, therefore, is in earlier hospitalization and more prompt institution of treatment. These steps seem imperative if we are to save many of the patients now dying of coma.—*Courtesy Diabetes Abstracts.*

PECK, F. B.

Penicillin, with special reference to its use in infections complicating diabetes. *Am. J. Med. Sci.* 208: 581, 1944.

The author treated 15 patients with diabetes mellitus complicated by infections by infiltrating solutions of penicillin in a concentration of 100 to 1000 units per cc. directly into the infected tissues. Administered in this manner, the drug seemed to be more effective than when in-

jected parenterally for systemic effect. The author suggests that this effectiveness may be due to the fact that the drug is introduced by infiltration at the site of bacterial action, a point which can not be reached by systemic medication when the circulation is inadequate. The dramatic results in two cases are emphasized by colored illustrations. No direct influence on the patient's requirement for insulin has thus far been observed. The author concludes that penicillin is an invaluable adjunct to treatment of infections caused by susceptible organisms, and is well adapted for use in the pyogenic infections, such as carbuncles, so frequently met as complications of diabetes mellitus.—*E.C.R., Jr.*

PRUNTY, F. T. G.

Reactive hyperinsulinism. *Brit. Med. J.* 2: 398. Sept. 23, 1944.

Attention is drawn to a condition which may be termed "reactive hyperinsulinism," as opposed to hyperinsulinism due to overactivity of the pancreas as a result of tumor of the islets. A case of "reactive hyperinsulinism," manifest by an excessive post-prandial fall of the blood-sugar level, is described. The study of the case revealed the following points: 1. Absence of low fasting blood sugar before breakfast and after exercise. 2. The marked post-prandial fall in blood sugar during the glucose tolerance test, accompanied by the onset of symptoms of hypoglycemia, together with an instability of the blood-sugar-regulating mechanism for a period of two hours. This finding is in close agreement with the history obtained of the most severe attacks occurring after the largest amounts of carbohydrate had been taken for tea. 3. A slight increase in the sensitivity to insulin, the occurrence of a typical hypoglycemic attack after intravenous administration of insulin, and the spontaneous return of the blood sugar level to normal limits with disappearance of the symptoms. 4. The mildness and ease of control of the symptoms by means of reduction in carbohydrate intake. 5. The family history of diabetes and renal glycosuria.—*R.B.G.*

RICHARDSON, R., M. A. BOWIE, J. EDEIKEN, I. H. LEOPOLD AND M. NAIDE

Diabetes mellitus as observed in 100 cases for 10 or more years. *Am. J. Med. Sci.* 209: 1. 1945.

The authors present a series of 4 papers analyzing this group of patients in terms of: I. general observations, II. cardiac studies, III. ocular findings, and IV. peripheral vascular findings in 89 of the patients. This analysis was undertaken because these patients have been under close supervision for many years at the University of Pennsylvania Hospital Clinic and because they have been maintained on a diet in which the carbohydrate has been increased (125 to 200 gm.) and the fat decreased (70 to 110 gm.), compared with diets previously in general use.

I. *General Observations* (*Richardson and Bowie*): 1) The age and race distribution in these patients was that usually found in diabetes. Sixty-nine of this group were over 50 years of age. In the entire series, the disease was present for from 10 to 25 years. 2) The severity of the disease did not progress in at least 45% during the ten year period. Ten patients required less insulin at the end than at the beginning of the period, and of the 55 who required more insulin, a number had also received increases in diet. 3) Acidosis occurred in only three of the group during the ten years of treatment, although it had occurred in 23 others prior to the ten year period. 4) While some evidence of generalized arteriosclerosis was present in 66 patients, it was sufficiently marked to be called an entity in only nine. 5) Twenty-six patients had anemia, but of these only three had less than 4 million R.B.C. and less than 13.5 gm. of hemoglobin per 100 gm. of blood. 6) Chronic or repeated acute infections occurred in 39 patients. Most frequently encountered were: cholecystitis (16 cases), pyelonephritis (9 cases) and tuberculosis (9 cases). 7) Of the whole group, 42% had slight or greater enlargement of the thyroid gland usually unaccompanied by physical signs. However, seven women developed hyperthyroidism and were operated on successfully. All of them showed some improvement of the diabetes after operation.

II. *Cardiac Studies* (*Edeiken*): 1) Hypertension (systolic blood pressure 160 mm. Hg.) was present in 38% of the cases, all of whom were past 50 years of age. The incidence of hypertension increased with each decade, was twice as common in women as men, and was independent of the duration, control and severity of the diabetes. 2) Definite cardiac enlargement was present in only ten of the hypertensives, an incidence of about one half that observed in non-diabetic hypertensives. 3) The greatest degree

of cardiac enlargement was observed in cases with ECG evidence of myocardial abnormality (with or without hypertension), and conversely there was a low incidence of ECG changes indicative of myocardial abnormality in the hypertensives without cardiac enlargement. 4) An ECG of the type frequently seen in hypertension and ascribed to left ventricular hypertrophy or left ventricular strain was not observed in any of the 38 cases with hypertension. 5) Only 3 (9.7%) of the patients under 50 had abnormalities of the heart which could be attributed to their diabetic state; all had had diabetes for over 15 years. 6) The low incidence of cardiovascular abnormalities in the younger group compared to similar studies in the literature on a high fat-low carbohydrate diet suggests the value of the high carbohydrate-low fat diet in reducing the incidence of premature cardiovascular abnormalities.

III. *Ocular Findings* (*Leopold*): 1) The closely controlled therapy of this series of patients resulted in: a) a reduced incidence of corneal wrinkles and complicated cataracts; b) a perhaps slightly reduced incidence of deep retinal hemorrhages and exudates (both of which tend to increase with the duration of the diabetes); c) an unchanged increased incidence of mobility of pigment, subcapsular "snowflake" cataracts, and superficial hemorrhages (which tend to increase with the duration of the diabetes); and d) not significantly different from that in the non-diabetic was the incidence of iritis, muscle palsies, optic neuritis, optic atrophy, senile type of lens change, and sclerosis. 2) Although arteriosclerosis, hypertension, renal disease, sepsis and hyperglycemia may all influence the incidence of deep punctate hemorrhages and waxy exudates, no one of them is the basic etiologic factor.

IV. *Peripheral Vascular Findings in 89 of These Cases* (*Naide*): 1) Three patients (11%) of those under 50 years of age, and 30 (34%) of those over 50 had evidence of peripheral arteriosclerosis. 2) Of the females, 42% had arteriosclerotic occlusive disease, as compared with 23% of the males. 3) Neuritis in the extremities was present in 31 of the 89 patients, chiefly in those with arteriosclerosis. 4) The severity of the diabetes did not affect the incidence of arteriosclerosis. 5) There were no amputations in the entire group.

V. *Final Summary* (*Richardson*): In 100 patients with diabetes mellitus of ten or more years' duration and with at least ten years of carefully supervised control by insulin and measured diets: 1) the severity of the diabetes did not increase in at least 45%; 2) the incidence of hypertension, infection, or ocular sclerosis was not influenced by the duration or the severity of the diabetes; 3) the incidence of deep retinal hemorrhages and exudates, and of superficial hemorrhages in the eyes was increased with the duration of the diabetes; 4) the incidence of cardiac enlargement in the diabetics with hypertension was about one half that observed in non-diabetic hypertensives; 5) the incidence of cardiovascular disease in patients under 50 years of age was lower than that previously found in diabetes; and 6) the incidence of arteriosclerotic occlusive disease of the lower extremities was much higher in diabetic women than in women without diabetes, and paralleled the greater frequency of coronary vessel disease in diabetic as compared with non-diabetic women.—*E.C.R., Jr.*

THOMAS, J. E., AND J. O. CRIDER

A further study of the innervation of the pancreas. The action of drugs of the atropine group. *Am. J. Med. Sci.* 208: 810. 1944.

The authors studied the secretory response of the pancreas to peptone, soap, or HCl in the intestine or to intravenous secretin in unanesthetized dogs before and after administration of atropine sulfate (0.2 mg./kg.) or of hyoscyamine hydrobromide (0.1 mg./kg.). The specific gravity and total nitrogen (mg./cc.) of the pancreatic juice were decreased by atropine or hyoscyamine regardless of the stimulus used to promote secretion. When the stimulus was soap, HCl or secretin, the volume of the secretion and the total nitrogen output were also reduced. When the stimulus was peptone, an increase in the volume of secretion usually followed the administration of either drug; the effect on total nitrogen was not constant but an increase was common. The authors point out: 1) the decreased response to secretin induced by the parasympathetic depressants is unexpected and contrary to the results obtained by others in anesthetized animals; 2) "tonic" cholinergic reflexes probably normally augment the response to secretin; 3) soap and HCl stimulate the pancreas in part through a nervous mechanism; and 4) the experiments provide no basis for conclusions regarding the mechanism through which peptone stimulates the pancreas.—*E.C.R., Jr.*

WHIPPLE, A. O.

Hyperinsulinism in relation to pancreatic tumors. *Surgery*, 16: 289. 1944.

It is obvious that the hypoglycemic state requires a careful search for the cause of the low blood sugar, and that hyperinsulinism must not be assumed to be the cause until lesions or disturbances in the liver, the pituitary, the adrenals, and the thyroid have been ruled out. In liver lesions causing hypoglycemia, the patients are gravely ill and show other obvious signs of liver damage. Similarly, the cases due to adrenal disease are not easily confused with hyperinsulinism, for the patients are usually seriously ill with Addison's disease or show signs of adrenal tumor. The low blood sugar levels associated with hypophyseal lesions are likely to cause more confusion, but they are usually associated with tumors causing headache and with visual field disturbances, and show x-ray evidence of widening or destruction of the sella turcica. In cases of hypoglycemia with hyperthyroidism, the basal metabolic rate is apt to be lower than in other cases of Graves' disease, and these patients may develop a thyroid storm after the removal of an islet tumor. For this reason, a basal metabolic determination should be done in all cases of suspected islet tumor; if the rate is above fifteen the patient should be given a course of iodine therapy, as in preparation for a thyroid operation. Finally, cases of epilepsy may mimic the syndrome of hyperinsulinism, because of the occurrence of "fits" or "spells." Electroencephalograms have proved of the greatest help in differentiating the epileptiform attacks from those seen in hyperinsulinism.

In reviewing the results of surgical therapy for islet tumors in this series, it is obvious that excision of adenomas and so-called questionably malignant tumors gives brilliant and lasting cures of the hypoglycemic state. On the other hand, in the majority of the patients in whom an islet-cell tumor was not discovered and a partial pancreatectomy was done, results were not good—either because a tumor was overlooked in the head of the organ or because an insufficient amount of the pancreas was removed. This is demonstrated by the fact that an overlooked tumor was found at the second operation in eight patients, four of whom had been explored here the first time and the other four in other clinics. The fact that seven of the overlooked tumors were in the head of the pancreas emphasizes the importance of an adequate exposure by a transverse incision, with mobilization of the duodenum so that all parts of the head of the organ can be carefully palpated. The recurrence or persistence of hypoglycemia below the 50-mg.-per cent level after a partial pancreatectomy is almost certain evidence of an overlooked islet tumor.—*Courtesy Diabetes Abstracts.*

PARATHYROID

MOEHLIG, R. C., AND H. W. ULCH

Multiple parathyroid adenomata. Three operative explorations with removal of two tumors. *Harper Hospital Bulletin* 2: 41. 1944.

A case is reported of a man, aged 62, who had had pulmonary tuberculosis 25 years before admission to the hospital, a left nephrotomy for the removal of multiple renal calculi 21 years before and subsequently developed a vesicle calculus with all the signs and symptoms of hyperparathyroidism. The first operation, at which only the right side of the neck was explored, resulted in the removal of a parathyroid adenoma. However, the symptoms persisted as did the hypercalcemia and the elevated serum phosphatase. A second operation seven weeks later failed to reveal a second parathyroid adenoma. Further studies were made, the patient meanwhile showing no improvement. At a third operation a large parathyroid tumor containing remnants of thymus tissue was found on the left side. The patient died shortly afterward with evidence of cardiac failure.—*R.H.G.*